Chapter 5
Reproductive Effects

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Introduction

Smoking harms many aspects of reproduction. An estimated 6 million women become pregnant each year in the United States, and more than 11,000 give birth each day (Ventura et al. 2000; Martin et al. 2002). Studies have shown that women who smoke are at an increased risk for a delay in becoming pregnant and for both primary and secondary infertility. Research has also shown that women who smoke during pregnancy risk complications, premature birth, low birth weight (LBW) infants, stillbirth, and infant mortality. LBW is a leading cause of infant deaths, numbering more than 300,000 deaths annually in the United States (Martin et al. 2002). Despite increased knowledge of the adverse health effects of smoking during pregnancy, only 18 to 25 percent of women quit smoking once they become pregnant. Data also suggest that a substantial number of pregnant women and girls continue to smoke (estimates range from 12 to 22 percent) (U.S. Department of Health and Human Services [USDHHS] 2001). This chapter reviews the evidence for a relationship between smoking and adverse reproductive effects. In particular, it examines the associations between smoking and fertility, smoking and pregnancy complications, and the health of children born to smokers.

Conclusions of Previous Surgeon General's Reports

Numerous previous reports of the Surgeon General on smoking and health have examined the effects of active smoking on the reproductive capabilities and outcomes for both men and women (Table 5.1). The 1964 Surgeon General's report (U.S. Department of Health, Education, and Welfare [USDHEW] 1964) identified an association between smoking during pregnancy and LBW (infants weighing <2,500 grams [g] at birth) that has been further explored in subsequent reports. The 1969 Surgeon General's report (USDHEW 1969) presented evidence on smoking during pregnancy and preterm delivery (<37 weeks completed gestation), spontaneous abortion, stillbirths, and neonatal mortality. The 1978 Surgeon General's report (USDHEW 1978) introduced new findings concerning smoking and pregnancy complications including placental abruption, placenta previa, and the premature rupture of membranes. The 1980 report on the health consequences of smoking for women (USDHHS 1980) extended previous findings on birth weight, retarded fetal growth, benefits of smoking cessation early in pregnancy, pregnancy complications, effects of smoking on the placenta, and mortality including sudden infant death syndrome (SIDS). This report also introduced new information on smoking risks and fertility, congenital malformations, and longer-term morbidity. The 1989 report (USDHHS 1989) evaluated new data and continued to find (1) a relationship between maternal smoking during pregnancy and lower birth weights, (2) higher rates of fetal and perinatal mortality associated with maternal smoking during pregnancy, (3) mixed findings on the relationship of maternal smoking to congenital malformations, (4) a higher risk of infertility among women and possibly men related to smoking, and (5) conflicting findings with regard to maternal smoking and longer-term physical development in the infant and child. The 1990 report on the health benefits of cessation (USDHHS 1990) noted that LBW could be reduced by 26 to 42 percent if smoking during pregnancy were eliminated. The 2001 report described findings on birth weight, infertility, ectopic pregnancy, spontaneous abortion, pregnancy complications, and SIDS (USDHHS 2001). That report also addressed smoking and breastfeeding, a topic not considered in this report. In prior reports, causal conclusions have been reached for a number of adverse reproductive outcomes (Table 5.1).

Table 5.1 Conclusions from previous Surgeon General's reports concerning smoking as a cause of reproductive effects

Disease and statement	Surgeon General's report
Low birth weight	
"Women who smoke cigarettes during pregnancy tend to have babies of lower birth weight." (p. 39)	1964
"New data are presented which confirm the finding that maternal smoking during pregnancy is associated with low birth weight in infants . . ." (p. 5)	1969
"Maternal smoking during pregnancy exerts a retarding influence on fetal growth as manifested by decreased infant birthweight and an increased incidence of prematurity, defined by weight alone." (p. 13)	1971
"Among all women in the United States, cigarette smokers are nearly twice as likely to deliver low birth weight infants as are non smokers." (p. 121)	1973
"A dose-response relationship exists between smoking and the incidence of low birth weight, preterm delivery, perinatal mortality, abruptio placentae, placenta previa, bleeding during pregnancy, and prolonged and premature rupture of the membranes." (p. 17)	1978
"There is abundant evidence that maternal smoking is a direct cause of the reduction in birth weight. . . . Birth weight is affected by maternal smoking independently of other determinants of birth weight. The more the mother smokes, the greater the baby's birth-weight reduction." (p. 1-21)	1979
"Babies born to women who smoke during pregnancy are, on the average, 200 grams lighter than babies born to comparable nonsmoking women." (p. 10)	1980
"There is a dose response relationship between maternal smoking and reduced birth weight: the more the women smokes during pregnancy, the greater the reduction in birth weight." (p. 10)	1980
"If a woman gives up smoking early during pregnancy, her risk of delivering a low-birth-weight baby approaches that of a nonsmoker." (p. 10)	1980
"Women who stop smoking before pregnancy or during the first 3 to 4 months of pregnancy reduce their risk of having a low birthweight baby to that of women who never smoked." (p. i)	1990
"Infants born to women who smoke during pregnancy have a lower average birth weight than infants born to women who do not smoke." (p. 307)	2001

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Table 5.1 Continued

Disease and statement	Surgeon General's report
Small for gestational age	
"...maternal smoking is associated with an increased incidence of prematurity defined by weight alone." (p. 5)	1969
"Overwhelming evidence indicates that maternal smoking during pregnancy affects fetal growth rate..." (p. 1-21)	1979
"Maternal smoking during pregnancy exerts a direct growth-retarding effect on the fetus; this effect does not appear to be mediated by reduced maternal appetite, eating or weight gain." (p. 11)	1980
"Although there is little effect of maternal smoking on [illegible] the proportion of fetal deaths and live births that occur before term [illegible] with maternal smoking level. Up to 14 percent of all preterm deliveries [illegible] rates may be attributable to maternal smoking." (p. 13)	1980
"Infants born to women who smoke during pregnancy ...are more likely to be small for gestational age than are infants born to women who do not smoke." (p. 307)	2001
Infertility	
"Studies in women and men suggest that cigarette smoking may impair fertility." (p. 12)	1980
"...the data suggest that impairment of fertility measured as delay in time to conception is related to smoking near the time of attempting to conceive and that smoking cessation prior to conception returns fertility to that of never smokers." (p. 358)	1990
"Women who smoke have increased risks for conception delay and for both primary and secondary infertility." (p. 307)	2001
Ectopic pregnancy	
"Women who smoke may have a modest increase in risks for ectopic pregnancy." (p. 307)	2001
Spontaneous abortion	
"...it appears that maternal smoking during pregnancy may be associated with an increased incidence of spontaneous abortion, stillbirth, and neonatal death and that this relationship may be most marked in the presence of other risk factors." (p. 5)	1969
"There is insufficient evidence to support a comparable statement for abortions (as for fetal deaths and stillbirths)." (p. 13)	1971

Table 5.1 Continued

Disease and statement	Surgeon General's report
"Perinatal mortality increases significantly with smoking as well as with other risk factors such as maternal age, parity, socioeconomic status, previous pregnancy history, and hemoglobin level." (p. 17)	1978
"The risk of spontaneous abortion, fetal death, and neonatal death increases directly with increasing levels of maternal smoking during pregnancy; interaction of maternal smoking with other factors which increase perinatal mortality may result in an even greater risk." (p. 1-1)	1980
"Cigarette smoking is now considered to be a probable cause of unsuccessful pregnancies..." (p. 20)	1989
"Women who smoke may have a modest increase in risks for...spontaneous abortion." (p. 307)	2001
Pregnancy complications	
"Maternal smoking increases the risk of fetal death through maternal complications such as abruptio placenta, placenta previa, antepartum hemorrhage, and prolonged rupture of membranes." (p. 1-22)	1979
"Increasing levels of maternal smoking result in a highly significant increase in the risk of abruptio placentae, placenta previa, bleeding early or late in pregnancy, premature and prolonged rupture of membranes, and preterm delivery - all of which carry high risks of perinatal loss." (p. 11)	1980
"The incidence of [illegible]ampsia is decreased among women who smoke during pregnancy; ho[illegible]reeclampsia develops in a smoking woman, the risk of perinatal mort[illegible]rkedly increased compared to preeclamptic nonsmokers." (p. 11)	1980
"Smok[illegible]m premature rupture[illegible]th a modest increase in risk for preterm delivery." (p. 307)	2001
"Women who smoke during pregnancy have a decreased risk for preeclampsia." (p. 307)	2001
Fetal deaths and stillbirths	
"There[illegible]ow that smoking mothers have a significantly[illegible]nancies due to stillbirth and neonatal death as com[illegible]m...(p. 3)	1971
"A strong, probably causal association between cigarette smoking and higher late fetal and infant mortality among smokers' infants is supported by the...evidence." (p. 134)	1973

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Table 5.1 Continued

Disease and statement	Surgeon General's report
"A strong, probably causal, association exists between cigarette smoking and higher late fetal and infant mortality among smokers' infants." (p. 17)	1978
"When adjustments are made for age, parity, differences in mothers, their socioeconomic status, and previous pregnancy histories, the risk of perinatal mortality attributable to smoking is highly significant, independent of these factors, and is dose related." (p. I-22)	1979
"The risk for perinatal mortality—both stillbirth and neonatal deaths—and the risk for sudden infant death syndrome (SIDS) are increased among the offspring of women who smoke during pregnancy." (p. 307)	2001
Infant mortality	
"*Maternal smoking increases the risk of fetal death through maternal complications* such as abruptio placentae, placenta previa, antepartum hemorrhage, and prolonged rupture of membranes. . . . Smoking . . . apparently contributes to the risk of their [smoking victims of the "sudden infant death syndrome"] demise. . . . Maternal smoking can be a direct cause of fetal or neonatal death in an otherwise normal infant." (p. I-22)	1979
"Excess deaths of smokers' infants are found mainly in the coded cause categories of '*unknown*' and '*anoxia*' for *fetal deaths*, and the categories of '*prematurity alone*' and '*respiratory difficulty*' for neonatal deaths. . . ." (p. 11)	1980
"An infant's risk of developing the 'sudden infant death syndrome' is increased by maternal smoking during pregnancy." (p. 11)	1980
"Cigarette smoking is now considered to be a probable cause of . . . increased infant mortality. . . ." (p. 20)	1989
Congenital malformations	
". . . no conclusions can be drawn about any relationship between maternal cigarette smoking and congenital malformations at present time." (p. 137)	1973
"The accumulated . . . data support a conclusion that maternal smoking increases the incidence of congenital malformations." (p. I-22)	1979
"There are insufficient data to support a judgement on whether maternal and/or paternal cigarette smoking increases the risk of congenital malformations." (p. 11)	1980
"Smoking does not appear to affect the overall risk for congenital malformations." (p. 307)	2001

Table 5.1 Continued

Disease and statement	Surgeon General's report
Impairment of children's development	
"According to studies of long-term growth and development, smoking during pregnancy may affect physical growth, mental development, and behavioral characteristics of children at least up to the age of 11." (p. I-21)	1979
"Maternal smoking during pregnancy may adversely affect the child's long-term growth, intellectual development, and behavioral characteristics." (p. 11)	1980
Low sperm quality	
"The available information suggests that current smoking is related to low sperm density. However, these data are limited." (p. 405)	1990

Sources: U.S. Department of Health, Education, and Welfare 1964, 1969, 1971, 1973, 1978, 1979; U.S. Department of Health and Human Services 1980, 1989, 1990, 2001.

Biologic Basis

The biologic basis of smoking and reproductive effects is complicated by how exposure is defined for reproductive effects, and is perhaps best discussed using a methodologic framework. When researchers examine the effects of smoking on reproductive outcomes, measuring exposure to smoking and adjusting *for possible confounding are two important* methodologic concerns. The critical exposure periods during gestation are brief for some adverse reproductive outcomes that have possible causal associations with active smoking. For example, when examining the relationship between smoking and congenital malformations, relevant data include exposure to tobacco smoke during the early part of pregnancy or during organogenesis. Similarly, for studying fetal growth restrictions, knowledge of smoking habits during the third trimester—the time when most of the growth in the fetus occurs—is of critical importance. However, in many studies the average amount smoked during pregnancy has been used as the exposure measure without collecting or reporting information sorted by the month of pregnancy or by the trimester.

For pregnancy outcomes, several potential confounding factors should be considered along with tobacco use, such as social class and racial and ethnic group. Among women of a lower social standing, not only are rates of smoking higher but rates of adverse pregnancy outcomes are also higher. Whereas lower social standing is thus a potential confounding variable, it may also be part of a common causal pathway *serving as one of the determinants of exposure to* smoking. Most recent studies do take potential confounders into account, and within the body of relevant literature, confounding has been adequately considered in the aggregate. However, for studies of some outcomes, such as those that examine associations of active smoking during pregnancy with child outcomes (i.e., physical, neurologic, and cognitive development), fully accounting for all potential confounders in the postpartum period is not feasible. The appropriateness of accounting for confounders will be discussed in each of the three sections that follow.

Another challenging issue that should be addressed is the mechanistic role of smoking in the causal pathway of adverse reproductive outcomes. For the role of smoking in preterm deliveries, for example, prenatal cigarette exposure might (1) increase the risk for pregnancy complications leading to a preterm

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delivery (e.g., the premature rupture of membranes), (2) decrease immune system functioning leading to an increased susceptibility to infections, or (3) act more directly through mechanisms not yet understood. Many studies do not capture data in a way that facilitates an adequate dissection of the underlying pathway. For example, few studies stratify analyses by the presence of pregnancy complications, and most such studies do not account for infections, as this purported risk factor for a preterm delivery has emerged only recently.

This methodologic challenge is further illustrated by SIDS, smoking during pregnancy, and the role of birth weight in the causal pathway. Because prenatal smoking results in lower birth weights and LBW is also a risk factor for SIDS, most studies account for birth weight, and some studies even limit the analyses to infants born weighing at least 2,500 g. It is unclear, however, that this analytic strategy is the most appropriate if the total contribution of smoking to the risk of SIDS is of interest. Only a few studies have examined the association between smoking and SIDS by stratifying the sample by birth weight.

Studies reviewed for this chapter were selected from a MEDLINE literature search from the mid-1960s to 2000, with some earlier studies identified through bibliographies. Title and abstract search terms included "smoking," and outcomes of interest such as "pregnancy," "fertility," "pregnancy complications," "birth weight," "preterm delivery," "cognitive development," "congenital malformations," "infant mortality," and "SIDS." For some searches (e.g., pregnancy complications), specific disorders were used as a search term (e.g., placenta previa). "Smoking" was also used as a Medical Subject Headings term, and review articles were consulted as additional sources for references.

As some of the topics presented in this chapter have been extensively investigated and the evidence found to support causality (e.g., smoking and birth weight), this chapter focuses on more recent studies and emerging areas such as male erectile dysfunction. When possible, recent studies were reviewed as the patterns of smoking among women of childbearing age and pregnant women have changed over the past few decades. In addition, the topic of smoking and cervical cancer is discussed in Chapter 2.

Fertility

Epidemiologic Evidence

Smoking and Sperm Quality

Cigarette smoking among men can affect spermatogenesis and sperm quality through hormonal and toxic influences. In a review of the literature on male reproduction and smoking, Vine (1996) noted that the cytotoxic effects of exposures to tobacco smoke may reduce the numbers and function of sperm, or may affect male reproductive hormone levels and lead to impairment of spermatogenesis. Although the results of studies supporting the latter mechanism are mixed, several studies have found that levels of testosterone, estradiol, estrone, androstenedione, and follicle-stimulating hormone are increased among smokers compared with nonsmokers (Barrett-Connor and Khaw 1987; Simon et al. 1992; Field et al. 1994; Vine 1996), while other studies have found decreases among smokers compared with nonsmokers or no differences between the two groups (Andersen et al. 1984; Barrett-Connor and Khaw 1987; Klaiber and Broverman 1988; Simon et al. 1992). Small sample sizes may partially explain the conflicting findings (Vine 1996) as larger studies tend to find increased levels of male reproductive hormones in smokers compared with nonsmokers (Simon et al. 1992; Field et al. 1994). Toxins found in tobacco smoke, such as cadmium, nicotine, lead, and radioactive alpha-particle emitting elements (internal emitters in particular), may be directly toxic as they circulate in the blood and reach the testes (Mattison 1982; Ravenholt 1982; Mattison et al. 1989; Oldereid et al. 1989).

In the following discussion, the studies examined associations between sperm production and male smoking and had larger sample sizes as well as some consideration of potential confounders. However, many of the studies on sperm quality included men seeking treatments for infertility, and the findings may have restricted generalizability. Also most do not adequately consider potential confounders such as abstinence, occupational exposures (e.g., teratogens and toxins in the workplace), or health behaviors (e.g., caffeine, alcohol, or drug use). Studies on smoking and

sperm quality have examined measures such as ejaculate volume and sperm output, density, viability, motility, and morphology (Vogel et al. 1979; Evans et al. 1981; Godfrey 1981; Andersen et al. 1984; Handelsman et al. 1984; Kulikauskas et al. 1985; Dikshit et al. 1987; Saaranen et al. 1987; Marshburn et al. 1989; Oldereid et al. 1989; Close et al. 1990; Holzki et al. 1991; Lewin et al. 1991; Chia et al. 1994) (Table 5.2). Handelsman and colleagues (1984) studied 119 healthy volunteer sperm donors and examined a variety of physical, demographic, and health behavioral factors and sperm quality. Although it is not clear how the category of smokers was defined, when compared with nonsmokers this group had a significantly reduced total sperm output (316 million versus 181 million sperm), motility (72 million versus 67 million sperm), motile sperm (235 million versus 127 million sperm), and total oval sperm (251 million versus 120 million sperm). These values were unadjusted for other factors. Marshburn and colleagues (1989) studied 445 men and reported a significantly reduced sperm volume for smokers compared with nonsmokers but no differences in sperm density, sperm motility, or the presence of abnormalities or dead sperm. The authors, however, warned against the confounding effect of coffee drinking in this and other studies. Chia and colleagues (1994) studied 618 men receiving treatment for infertility and reported means for volume, density, motility, and morphology adjusted for age, medical history, occupational exposure to cigarette smoke, and testicular size. Current smokers had a lower sperm density, a lower proportion with normal morphology, and a higher proportion with head defects than nonsmokers (lifetime nonsmokers and former smokers). Most studies have not found dose-response relationships with the amount smoked, and a number of studies found no difference in sperm quality between smokers and nonsmokers (Saaranen et al. 1987; Oldereid et al. 1989; Close et al. 1990; Holzki et al. 1991; Lewin et al. 1991). One large study found no differences between those exposed to tobacco smoke and chewing and those not exposed to tobacco smoke and chewing (Dikshit et al. 1987).

A meta-analysis of 20 different study populations conducted by Vine and colleagues (1994) found that sample size was a major contributor to apparent inconsistencies among the study findings. Overall, the weighted estimate of reduction in sperm density among smokers compared with nonsmokers was 13 percent (95 percent confidence interval [CI], 8.0–21.0) adjusted for population source, minimum number of cigarettes smoked by smokers, number of specimens analyzed, and whether laboratory staff were blinded to the status of the participants (Vine et al. 1994). This estimate is somewhat lower than that of an earlier review of 10 studies, which found a reduction in smokers compared with nonsmokers to be 22 percent.

In summary, studies on the association between smoking and sperm quality have produced conflicting findings. Many studies have small sample sizes comprised of men who may have problems with infertility unrelated to smoking. And despite comments about similarities between smokers and nonsmokers, few included adjustments for potential confounders such as sexual abstinence, occupational exposures, and health practices of participants (e.g., consumption of alcohol, caffeine, or drugs). Nonetheless, the evidence suggests that smokers may have decreased semen volume and sperm number and increased abnormal forms, although any clinical relevance of these findings is not clear.

Smoking and Fertility in Women

Numerous studies have shown that smoking results in reduced fertility and fecundity for couples with one or both partners who smoke (Table 5.3). Fertility might be reduced by active smoking through numerous mechanisms. Animal studies suggest that prenatal exposure to polycyclic aromatic hydrocarbons has a destructive effect on oocytes and may affect the release of gonadotropins, corpora lutea formation, gamete interaction, and implantation. Studies in rats and humans also have shown that postfertilization cleavage is delayed in smokers (Mattison et al. 1989; Hughes et al. 1992; Rowlands et al. 1992). In the rat, nicotine delays implantation of the fertilized ovum, but whether this delay affects fertility remains to be determined. Smoking also has been shown to affect menstrual function by shortening cycles and increasing anovulation, which may also contribute to subfecundity and infertility (Windham et al. 1999).

The literature uses a number of different indicators to measure fertility and fecundity. Infertility in the United States is defined as the inability to conceive for 12 months; the World Health Organization uses failure to conceive for 24 months or more. Primary infertility refers to women who have not had prior pregnancies while secondary infertility concerns women who have been pregnant before. Unfortunately, the literature on smoking and fertility among women does not consistently employ these standard measures.

Laurent and colleagues (1992) studied primary infertility in 2,714 cases and controls. Primary infertility was associated with smoking more than one pack per day compared with nonsmokers (odds ratio

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[OR] = 1.36 [95 percent CI, 1.14–1.61]) and starting to smoke before 18 years of age compared with nonsmokers (OR = 1.30 [95 percent CI, 1.0–1.68]). These estimates were adjusted for education, age, race, and history of ovarian disease. Joffe and Li (1994) examined the time to first pregnancy among 3,132 women. After adjusting for age, education, and smoking status of the father in a Cox survival model, women who smoked before conception were less likely to become pregnant than nonsmokers; the risk ratio for time to pregnancy for women who smoked was 0.89 (95 percent CI, 0.83–0.97). Alderete and colleagues (1995) studied 1,341 primiparas and reported that women who smoked, regardless of whether they drank coffee, had about one-half the fertility (OR = 0.5 to 0.6 for conception times of 6 and 12 months) of nonsmokers who did not drink coffee.

As early as the 1960s, an association between smoking and decreased fertility was observed. In a sample of 2,016 women in Tennessee, women who smoked had a 46 percent higher rate of infertility than women who did not smoke (Tokuhata 1968). In a large prospective family planning study of more than 17,000 women, which included 6,199 episodes of contraceptive stoppage for the purpose of becoming pregnant, Howe and colleagues (1985) demonstrated a dose-response relationship between the amount of current smoking and reduced fertility that was based on pregnancy rates five years after terminating contraception. Women who smoked more than 20 cigarettes per day had their fertility reduced by 22 percent compared with lifetime nonsmokers and former smokers. Lighter smokers (<15 cigarettes per day) did not show demonstrable reductions in fertility. Although this study did not adjust for potential confounders, reduced fertility in smokers did not vary significantly by social class. Suonio and colleagues (1990) demonstrated a dose-response relationship between any current smoking and a delay to conception for short (6-month) and long (18-month) periods of time. In this sample of 2,198 mothers interviewed at 20 weeks of gestation, with adjustments for several confounders (age, prior pregnancies, prior terminations and spontaneous abortions, alcohol consumption, occupation of the mother, employment, smoking status and alcohol consumption of the father), the OR of conception delay for smokers (>four cigarettes per day) compared with nonsmokers at six months was 1.6. Conception delays continued for smokers (any smoking) compared with nonsmokers at 12 and 18 months after discontinuing contraception. Women who smoked more than four cigarettes per day had a 2.1 OR for conception delay at 18 months compared with nonsmokers. Dose-response relationships were demonstrated for lighter and heavier smokers for most outcomes (Suonio et al. 1990).

In a large multicountry study, Bolumar and colleagues (1996) examined the association between smoking and time to pregnancy that exceeded nine and one-half months in two large samples: (1) a population-based sample of women aged 25 through 44 years and (2) a sample of pregnant women recruited from prenatal clinics. Each sample had more than 4,000 couples. The OR was 1.7 (95 percent CI, 1.3–2.1) for a longer time to pregnancy for women smoking 11 or more cigarettes per day compared with nonsmokers in the population sample. For current pregnancy in the pregnant sample, the OR was also 1.7 (95 percent CI, 1.3–2.3), demonstrating a dose-response relationship for this outcome. Women who smoked 1–10 cigarettes per day had an OR of 1.4 in the population sample (95 percent CI, 1.1–1.7) and also in the pregnant sample (95 percent CI, 1.0–1.8). In the population-based sample, associations were also examined for the most recent pregnancies. For the most recent wait time, women who smoked 11 cigarettes or more per day compared with nonsmokers had an OR of 1.6 (95 percent CI, 1.3–2.1). ORs in this study were adjusted for age, coital frequency, education, oral contraceptive use, and coffee consumption (Bolumar et al. 1996). Curtis and colleagues (1997) reported a decreased fecundability (the monthly probability of conception), measured by time to pregnancy after discontinuing contraception, among smokers compared with nonsmokers. The fecundability ratio of smokers was 0.90 (95 percent CI, 0.81–0.95), and a dose-response relationship was observed for heavier smokers. Fecundability ratios for those smoking 11–20 cigarettes and more than 20 cigarettes per day were 0.87 (95 percent CI, 0.77–0.99) and 0.74 (95 percent CI, 0.59–0.92), respectively. Curtis and colleagues (1997) also reported associations with spousal smoking habits. Compared with both partners who were nonsmokers, when both the woman and her spouse smoked the fecundability ratio was 0.77 (0.68–0.86). In their study of 678 pregnant women, Baird and Wilcox (1985) reported that smokers had 3.4 times the risk of taking more than one year to conceive than nonsmokers, and heavy smokers showed an even greater reduced fertility than light smokers. In a review of 13 studies on this topic, Hughes and Brennan (1996) reported that all but one study found a reduced fecundity among smokers compared with nonsmokers.

Table 5.2 Studies on the association between smoking and sperm quality

Study	Study period	Population	Definition of smoking
Vogel et al. 1979	NR*	474 men	Smokers and nonsmokers (242 nonsmokers and 232 smokers)
Evans et al. 1981	NR	86 men	Number of cigarettes/day (0, <15, 15–25, >35) (43 smokers of ≥1 cigarette/day and 43 nonsmokers)
Godfrey 1981		344 men	• Nonsmokers • Smokers: ≤20 and >20 cigarettes/day
Andersen et al. 1984	1977–1981	253 men and 230 women referred to an infertility clinic	Smokers: ≥10 cigarettes/day
Handelsman et al. 1984	NR	119 healthy men presenting for screening as potential sperm donors	Smokers: 6 current and former
Kufikacskas et al. 1985	NR	253 men aged 19–32 years	• Smokers: ≥1 cigarettes/day for at least the last 5 years • Nonsmokers had never smoked or had not smoked for at least 5 years
Barrett-Connor and Khaw 1987	1972–1974 1985–1986	590 men aged 50–79 years without a history of cardiovascular disease	Never/former/current smokers were classified at time of interview: • 176 never smokers • 304 former smokers • 110 current smokers (<10, 11–20, >20 cigarettes/day)
Dikshit et al. 1987	July 1985–September 1986	626 male partners aged 20–34 years of couples undergoing idiopathic infertility	• Nonusers: no tobacco use in any form • Smokers: >10 cigarettes/day • Tobacco chewers: >10 helpings/day (288 nonusers, 219 smokers, and 119 tobacco chewers)

*NR = Data were not reported.

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Key results
• Smoking may be correlated with gonadal function and with particular central nervous system functions influenced by gonadal hormones • Smokers had less gonadal hormone stimulation than nonsmokers • Differences were observed only in smokers who started smoking at 15 years of age or younger (early smokers), compared with late smokers who were older than 15 years of age when they began
• An examination of mor[illegible] abilities in sperm samples revealed that smokers had a significantly greater percentage of ab[illegible] nonsmokers • There was no clear qua[illegible] between the degree of abnormality and the number of ciga rettes smoked • Sperm abnormalities in cigarette smokers may reflect genetic damage as a consequence of cigarette smoke
• Sperm morphology did not differ significantly among the three groups • No differences in sperm motility • No significant differences in sperm counts
• Male smokers [illegible] higher serum testosterone levels and lower semen volumes while fathering children; [illegible] cortisone, and sperm density, motility, and morphology did not differ between smokers [illegible] • Cigarette smo[illegible] central dopaminergic tonus and reduce serum prolactin levels, but the biologic significance of this finding to reproductive functions is unknown
• Smoking was associated with a highly significant reduction in sperm output and motility • Sperm density and output as well as the equivalent parameters for motile and morphologically normal sperm were lower in smokers than in nonsmokers • Semen volume or the percentage of abnormal forms did not differ between the two groups
• Spermatozoa from smokers possessed significantly decreased density and motility compared with nonsmokers • Individual sperm counts indicated more than twice as many smokers as nonsmokers had a sperm density of $<60 \times 10^6$ sperm/mL, considered to be the lower limit of the normal range • Morphologic abnormalities appeared to be more prevalent among smokers, but did not differ significantly
• Current cigarette smokers had significantly higher mean endogenous androstenedione, estrone, and estradiol levels compared with nonsmokers • Among smokers, a dose response relationship was apparent for these hormones, with mean levels increasing with increased cigarette use
• Results failed to demonstrate a significant influence of tobacco use (smoking or chewing) on seminal parameters • Although there was a reduction in volume, sperm density, and total count among tobacco users, the differences were statistically insignificant • Tobacco use was not associated with impaired sperm quality in males selected from an idiopathically hypofertile population

Table 5.2 Continued

Study	Study period	Population	Definition of smoking
Saaranen et al. 1987	NR	190 men of reproductive age with no previous history of infertility	• Nonsmokers • Occasional smokers (1–15 cigarettes/day) • Regular smokers (≥16 cigarettes/day)
Dai et al. 1988	1983–1986	• Longitudinal study: 121 men from the Multiple Risk Factor Intervention Trial (MRFIT) • Case-control study: 163 MRFIT men who developed coronary heart disease, and 163 matched controls	Smokers averaged 34 cigarettes/day
Marshburn et al. 1989	1978–1982	345 men	None, <20 cigarettes/day, and >20 cigarettes/day
Olshan et al. 1989	NR	301 men aged 20–58 years under fertility investigation	• Moderate smokers: 1–14 cigarettes/day • Heavy smokers: 15–40 cigarettes/day (203 smokers, 147 nonsmokers)
Close et al. 1990	NR	164 men from infertile couples referred to a urologic fertility clinic	• Number of packs/day • Nonsmokers included former smokers
Hjollund et al. 1991	1981–1987	90 men retrospectively selected from an infertility clinic	• Nonsmokers had never smoked • Smokers: >10 cigarettes/day (50 smokers, 40 nonsmokers)
Lewin et al. 1991	November 1986–February 1988	675 men aged <45 years under infertility investigation	Smokers: >10 cigarettes/day (293 smokers, 382 nonsmokers)

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Key results
• Sperm output was normal in both smokers and nonsmokers, but semen volume was smaller in heavy smokers than in nonsmokers • Percentage change in sperm motility during 24 hours was different in men with different smoking habits: initially, sperm motility was better in heavy smokers than in those who smoked <16 cigarettes/day; the motility decreased more rapidly for heavy smokers than for nonsmokers, and the rapid decrease in the survival spermatozoa in smokers may be harmful with respect to fertility
• Serum total and free testosterone concentrations were positively correlated with cigarette smoking among the longitudinal sample and controls but not for the baseline serum from the coronary heart disease cases • There was no association between either serum testosterone concentrations and cigarette smoking in this population
• Individuals who drank >4 cups of coffee/day and smoked >20 cigarettes/day had a lower proportion of motile spermatozoa and a higher proportion of dead cells compared with nonsmokers who did not drink coffee • The effects of smoking on seminal volume, and of coffee drinking on sperm density, did not appear to be dose dependent
• There were no significant differences in any aspect of sperm quality including DNA distribution among nonsmokers, moderate smokers, and heavy smokers • Using conventional parameters, the study did not show that smoking has deleterious effects on sperm quality
• Current cigarette smokers, marijuana users, and heavy alcohol users showed greater numbers of leukocytes in the seminal fluid than did nonusers • Cigarette smokers had lower sperm penetration assay scores than nonsmokers (median: 2.5 vs. 8.0, respectively) • Compared with nonusers of cigarettes, users of marijuana or alcohol showed no decrease in sperm counts or motility, or in the percentage of oval sperm
• Smokers had sperm volumes significantly smaller than nonsmokers of the same age • No additional effects on sperm parameters were found • Cigarette smoking revealed no detrimental effect on spermatogenesis
• An overall reduction of sperm concentrations was seen in smokers compared with nonsmokers in relation to the effects of the number of cigarettes/day and number of pack-years (the number of years of smoking multiplied by the number of packs smoked per day) calculated to measure the cumulative effects of smoking • No differences were observed in sperm motility and sperm penetration assay • In men <45 years of age with sperm analyses showing motility >30%, concentration >10 x 10^6/mL, and normal morphology, smoking was not detrimental to fertility

Table 5.2 Continued

Study	Study period	Population	Definition of smoking
Chia et al. 1994	January 1991–June 1992	618 men undergoing infertility screening	• Nonsmokers had never smoked a cigarette or had quit for more than a year • Current smokers

Not all studies have reported positive associations between smoking and reduced fertility. A prospective study of fertility conducted by de Mouzon and colleagues (1988) with 1,887 couples found that reduced fertility associated with smoking was no longer statistically significant once possible confounders (method of birth control, attempting to conceive, oral contraceptive use as the most recent method, social class, prior deliveries, and year) were included in the analyses. Specifically comparing smokers with nonsmokers, cigarette smoking by the woman produced a 0.86 rate of relative fertility (95 percent CI, 0.63–1.19) and by the man a rate of 0.99 (95 percent CI, 0.85–1.14) after accounting for oral contraceptive methods, previous deliveries, social class, and prior attempts to conceive.

An increasing number of studies have used couples seeking treatment for infertility. These studies have consistently shown that treatment success is affected by smoking. Several studies documented that the success of in vitro fertilization (IVF) is significantly reduced among smokers compared with nonsmokers (Elenbogen et al. 1991; Pattinson et al. 1991; Hughes et al. 1992; Rosevear et al. 1992; Rowlands et al. 1992; Van Voorhis et al. 1996; El-Nemr et al. 1998), but other studies have not shown this reduction (Trapp et al. 1986; Sharara et al. 1994; Sterzik et al. 1996). Joesbury and colleagues (1998) examined the association of smoking by both partners with the likelihood of pregnancy within 498 consecutive IVF treatment cycles. Although female smoking had no association, male smoking was associated with a reduction in the probability of achieving a 12 week pregnancy. This study observed that age did modify the effect of smoking. For every one-year increase in age, there was a 2.4 percent reduction in the probability that the man's partner would achieve a 12-week pregnancy (Joesbury et al. 1998). The authors suggest that pre-zygotic genetic damage is the mechanism causing these reductions in a successful pregnancy.

Evidence Synthesis

Although mechanisms for an effect of smoking on sperm quality have been proposed, study findings are inconsistent for an association between active smoking and sperm quality. Some studies have shown positive associations, with a few demonstrating dose-response relationships with the amount smoked; others find no association. Many of the studies have potential flaws related to participant selection and confounding.

The evidence for a positive association between active smoking and subfertility and subfecundity in women consistently shows that active cigarette smoking reduces fecundity and increases the risk of primary infertility. The number of studies is substantial and various study designs and outcome measures have been used. Several studies demonstrated a dose-response relationship with the number of cigarettes smoked. Although the evidence is less consistent in

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Key results
• Smokers had a significantly poorer sperm density, a lower percentage of sperm with normal morphology, and a higher percentage of headpiece spermatozoa defects compared with nonsmokers • Cigarette smoking appeared to affect sperm density and spermatozoa morphology, especially the headpiece • A dose-response relationship between cigarette smoking and spermatogenesis is suggested based on calculated cigarette-years (the number of years of smoking multiplied by the number of cigarettes smoked per day): 0, 1–199, ≥200 • Sperm density (10^6/mL) shows a decreasing trend as cigarette-years increase. Differences are significant ($p < 0.0001$) even after using ANCOVA to adjust for medical history, occupational exposure, age, and testicular volumes

studies examining the impact of smoking on the success of IVF, these studies may be limited by inadequate adjustment for fertility-related confounders. Moreover, animal and human studies are beginning to provide an understanding of the mechanisms by which cigarette smoke or its components affect fertilization in females, pointing to the plausibility of this association. The evidence reviewed shows consistency, dose-response relationships, and appropriate temporality, and partially characterizes the mechanistic basis. Based on the evidence through 2000, the 2001 Surgeon General's report concluded that "women who smoke have increased risks for conception delay and for primary and secondary infertility" (USDHHS 2001, p. 307).

Conclusions

1. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and sperm quality.
2. The evidence is sufficient to infer a causal relationship between smoking and reduced fertility in women.

Implications

Regarding smoking and sperm quality, future studies should also include more samples of men not seeking treatment for infertility, larger study populations, and the information to adjust for potential confounding factors such as occupational exposures (e.g., teratogens and toxins in the workplace) and health behaviors (e.g., caffeine, alcohol, or drug use). Women intending to become pregnant should be warned that their smoking reduces fertility; health care workers should be aware of the causal association of smoking by women with reduced fertility.

Table 5.3 Studies on the association between smoking and fertility in women

Study	Study period	Population	Definition of smoking
Tokuhata 1968	NR[a]	2,016 women from a death registry	• Number of cigarettes smoked • Tobacco habits data included chewing tobacco and using snuff
Baird and Wilcox 1985	1983	678 pregnant women who had stopped using birth control in order to get pregnant	• Smokers: ≥1 cigarette/day during at least the first month after stopping birth control • Nonsmokers: all others
Howe et al. 1985	1968–1974	17,032 white married women, aged 25–39 years, from the Oxford Family Planning Association contraceptive study	• Never smoked • Former smokers • Current smokers stratified by cigarettes/day (1–5, 6–10, 11–15, 16–20, >20)
Trapp et al. 1986	1984–1985	114 patients who underwent IVF[b]	Smokers or nonsmokers
de Mouzon et al. 1988	1977–1982	1,887 couples	• Nonsmokers did not smoke • Smokers: ≥1 cigarette/day
Sufanio et al. 1990	1983	2,198 mothers 20 weeks pregnant	• Nonsmokers • Light smokers (1–4 cigarettes/day) • Heavy smokers (>4 cigarettes/day)
Elenbogen et al. 1991	NR	41 women aged <37 years suffering from mechanical infertility	• Nonsmokers • Smokers: >15 cigarettes/day

[a]NR = Data were not reported.
[b]IVF = In vitro fertilization.
[c]OR = Odds ratio.

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Key results
• Cigarette smokers had increased risks of infertility, reduced frequency of pregnancies, and an increased risk of fetal losses • Risks of infertility and fetal losses were higher in those who developed breast and genitalia cancer, but were not further increased by smoking • In contrast, the risks were lower in those with noncancerous diseases, but were elevated by smoking • The husband's smoking history was independent of the association between the wife's smoking and reproductive histories
• Smokers were 3.4 times more likely to have taken more than a year to conceive compared with nonsmokers • Fertility of smokers was estimated to be 47% of that for nonsmokers • Heavy smokers experienced lower fertility rates than light smokers (67% and 75% of the pregnancy rate of nonsmokers, respectively) • Fertility was not affected by the husband's smoking
• There was an inverse relationship between the age at stopping contraception and fertility, in both nulliparous and parous women, but the effect was greater in nulliparous women • There was a *dose-response relationship* between smoking and *decreased fertility*: more cigarettes/day were associated with decreased relative fertility rates
• There were no significant differences in IVF outcomes (fertilization and pregnancy rates) between smokers and nonsmokers • The shedaride (SCN) concentrations in serum and follicular fluid were higher in smokers than in nonsmokers • The influence of smoking on IVF is difficult to ascertain; IVF methods need to improve
• Cigarette smoking by both spouses was related to decreased fertility when considered independently, but the association did not remain significant when confounding variables were controlled • The relationship between tobacco and subfertility is not clear, and if it exists, is very low • The effects of tobacco on fertility found by different studies may be explained by behavioral factors related to tobacco use
• A significant deleterious effect of smoking on fecundity was observed, which increased with longer delays in conception • The OR[1] shifted from 1.1 at 6 months to 3.8 at 18 months for those who smoked 1–4 cigarettes/day; and from 1.8 to 2.0 for smokers of >4 cigarettes/day • Among [illegible] 12 months, both maternal and paternal smoking increased [illegible] (1.3, respectively), and the effect was potentiated by active [illegible]
• Follicular fluid levels of estradiol were significantly lower in smokers than in nonsmokers • Fertilization rates were lower for smokers (40.9 vs. 61.7%) • Cigarette smoking had a detrimental effect on IVF and embryo transfer

Table 5.3 Continued

Study	Study period	Population	Definition of smoking
Pattinson et al. 1991	March 1984–March 1989	447 couples seeking IVF[1]	Both partners were asked if they smoked and if so, how many cigarettes/day
Hughes et al. 1992	March 1990–May 1991	222 couples undergoing consecutive IVF and embryo transfer	Women were classified as nonsmokers, smokers of 1–14 cigarettes/day, and smokers of >15 cigarettes/day
Laurent et al. 1992	December 1980–April 1983	2,714 randomly selected women aged 20–54 years; 483 had primary infertility and 2,231 served as controls	Smokers began smoking cigarettes before or during the period of unprotected intercourse (for the infertile cases) or before the first conception (for the controls)
Rosevear et al. 1992	1986–1991	45 women with tubal and other complications of infertility	Smoking determined by [illegible] levels of nicotine metabolites (less or [illegible] ng/mL) in ovarian follicular fluid
Rowlands et al. 1992	NR	Couples who received IVF	Smoking histories for both partners were recorded
Joffe and Li 1994	1958–1991	11,407 persons: 3,132 female and 2,576 male cohort members who had borne or fathered at least 1 live birth	Current smoking habits of the cohort [illegible] partners, and [illegible] of the cohort [illegible] months before [illegible] each [illegible]
Sharma et al. 1994	January 1991–December 1992	210 women from a general infertile population with 102 undergoing IVF	• Nonsmokers had never smoked cigarettes • Current cigarette smokers • Former smokers not currently smoking were excluded

IVF = In vitro fertilization.
[1]CI = Confidence interval.

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Key results
• There were no significant differences between smokers and nonsmokers in peak estradiol levels, the number of eggs retrieved, or fertilization or implantation rates • The incidence of spontaneous abortion was higher in smokers (42%) than in nonsmokers (19%); consequently, the delivery rate per IVF cycle was significantly lower in smokers (11 of 124, 9%) than nonsmokers (40 of 236, 17%) • There was no effect when only the husband was a smoker
• There were no differences in ovarian stimulation, peak estradiol levels, or the number of oocytes retrieved • Heavy smokers had higher fertilization rates than [illegible]ers (79.3 vs. 61.3%) • The rate of embryo cleavage was regarded [illegible] fashion; in smokers of 1–14 cigarettes/day, the likelihood of transferring an embryo [illegible] 0.87 (95% CI*, 0.56–1.4); and in smokers of ≥15 cigarettes/day, the likelihood was 0.52 (9[illegible] • No significant differences were noted in clinical outcomes following embryo transfer
• Smoking 1 pack/day (OR = 1.36) and starting to smoke (OR = 1.3) were significantly associated with increased infertility • Smoking did not significantly increase the time required to conceive among infertile women • Women should stop smoking when they are attempting to become pregnant
• Smoking (57%) is associated with reduced fertilization of eggs to about two thirds of the normal rate for nonsmokers (75%) • The median fertilization rates for high vs. l[illegible] nine groups were 57% and 75%, respectively • Analysis of individual fertilization rates g[illegible]ears of 1986 (range 0–100) for the cotinine undetectable group, and 57% (0–102) for the cotinine-d[illegible] group (p = 0.01, Kruskal-Wallis) • Women should be advised to stop or redu[illegible]ng generally, especially before IVF
• There was a significant difference in fertilization rates among couples who were nonsmokers, female only smokers, male only smokers, and both smokers • Reduced numbers of mature oocytes and reduced pre-ovulatory estradiol concentrations were seen in the partners of men who smoked, but the differences were not significant
• Both the time to pregnancy and clinical subfertility were associated with smoking habits and educational levels of both partners • A multivariate analysis showed that paternal smoking failed to enter the model if educational variables were also included (p > 0.05 did not meet the criteria for inclusion) • Maternal smo[illegible] earlier reports of an apparent effect of paternal smoking may be due to confounding
• Smokers had an increased prevalence of diminished ovarian reserves (12.31%) compared with age-matched nonsmoking controls (4.83%) • Smokers with normal ovarian reserves had ovarian responses and pregnancy rates equivalent to nonsmoking controls • A diminished ovarian reserve may be a principal mechanism reducing fecundity among women who smoke cigarettes

Table 5.3 Continued

Study	Study period	Population	Definition of smoking
Alderete et al. 1995	1959–1966	1,341 women who were primigravidas	• Smokers: ≥1 cigarette/day after discontinuing contraception • Nonsmokers: gravidas who had never smoked • To assess dose responses, light = 1–9 cigarettes/day, moderate = 10–19, heavy = ≥20
Bolumar et al. 1996	August 1991 – February 1993	• Wom[illegible] 6–44 years [illegible] of couple[illegible] analy[illegible] couple • W[illegible] 20 weeks [illegible] prenatal visits [illegible] analysis was a[illegible] • More [illegible] couples in each [illegible]	• Cigarettes/day (1–10, >11) • For male partners, dichotomous data on smoking (yes/no) were available
Sterzik et al. 1996	NR	197 women aged 23–39 years from an IVF[1] program	• Nonsmokers: cotinine concentrations <20 ng/mL • Passive smokers[2]: cotinine concentrations >20 ng/mL and <50 ng/mL • Active smokers: cotinine concentrations >50 ng/mL (68 nonsmokers, 26 passive smokers, 103 active smokers)
Van Voorhis et al. 1996	January 1989–July 1994	498 women treated at an assisted reproductive technologies program	• Smoking was determined by asking if women ever smoked and if yes, number of years (current cigarettes multiplied by years the was ascertained • Nonsmokers (had never smoked) • Former smokers (had quit before their cycle) • Current (smoked during their assisted reproductive cycle)

[1]IVF = In vitro fertilization.
[2]Exposed to someone else's tobacco smoke.

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Key results
• Smokers had about one-half the fertility (OR = 0.5–0.6) of nonsmokers and noncoffee drinkers for times to conception of 6 and 12 months, regardless of whether they drank coffee • Nonsmoking coffee drinkers did not have decreased fertility compared with nonsmokers who did not drink coffee (adjusted OR = 1.0–1.2) • Coffee drinking did not further increase the risk of delayed conception among smokers over the risk posed by smoking (OR = 0.6–0.8)
• Female smok[illegible] with subfecundity both with the first pregnancy (OR = 1.7) and during the most recent w[illegible] conceive pregnancy (OR = 1.6) • No significant association was found with male smoking
• There were no significant differences in fertilization and pregnancy rates among nonsmokers, passive smokers, and active smokers • The serum estradiol levels were decreased significantly in women who smoked when compared with nonsmokers and passive smokers; decreased serum estradiol concentrations were not associated with adverse effects on fertilization and pregnancy rates in smokers • There was no clinically detectable impairment of fertilization potential attributable to female smoking, and other factors have a greater influence on IVF outcomes
• Current and former smokers had reduced gonadotropin-stimulated ovarian function compared with nonsmokers • Increased tobacco exposures were associated with decreased serum estradiol concentrations, decreased number of retrieved oocytes, and fewer embryos obtained • Women who smoked during their treatment cycle had a 50% reduction in implantation and ongoing pregnancy rates, compared with never smokers • Cigarette smoking was associated with prolonged and dose-dependent adverse effects on ovarian function

Table 5.3 Continued

Study	Study period	Population	Definition of smoking
Curtis et al. 1997	1991–1992	2,607 planned pregnancies over the previous 30 years	• Nonsmokers did not smoke (former smokers who had quit smoking as of the year they started trying to conceive were treated as nonsmokers, except in analyses requiring former smokers to be examined separately) • Smoking was stratified by cigarettes/day (0, 1–5, 6–10, 11–20, >20) and pack-years (0, 0–5, >5–10, >10) • Data were also collected on ever smoked, current smoking habits, number of years smoked; and for those who quit, the year of cessation
El-Nagar et al. 1998	9-month period in 1995	173 women undergoing IVF-embryo transfer cycle at a fertility center	• 108 nonsmokers, 65 smokers at the time of the interview • Cigarettes/day
Joesbury et al. 1998	January 1994–December 1995	385 couples, 498 IVF treatment cycles	• Nonsmokers included never and former smokers • Current smokers
Hull et al. 2000	April 1991–December 1992	11,893 pregnant women	• Cigarettes/day • Smokers were active, passive, or both

IVF = in vitro fertilization

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Key results

- Cigarette smoking among women and men was associated with decreased fecundability (fecundability ratio 0.90 and 0.88, respectively)
- Caffeine consumption among women was not associated with decreased fecundability, even in higher amounts
- Alcohol use among women and men was not associated with fecundability

- Cigarette smoking in women appeared to significantly reduce their ovarian reserve and lead to poor responses to ovarian stimulation at an earlier age
- Women who [illegible] basal follicle stimulating hormone concentration and reported a higher mean [illegible] of ovarian stimulation than nonsmokers
- Compared with [illegible] had a lower mean number of oocytes, and higher rates of abandoned cycles [illegible] fertilization failure
- The difference [illegible] luteal pregnancy rate per cycle, 16.9% for smokers vs. 21.3% for nonsmokers, was not statistically significant

- Male smoking interacted with age and was associated with a 2.4% decrease in the likelihood of achieving a 12-week pregnancy with every 1-year increase in age
- Ovarian reserves diminished with increasing age more significantly for female smokers than for nonsmokers
- The study failed to show that there was an elevated incidence of pregnancy loss among female smokers

- Active smoking by women was significantly associated with failure to conceive at >6 months (OR = 1.23 [95% CI: 0.98–1.54]) and at >12 months (OR = 1.54 [95% CI: 1.19–2.01]) after adjusting for confounding factors
- Compared with women who did not smoke, female passive smokers had significantly delayed conception [illegible] = 1.17 [95% CI: 1.02–1.37]) and >12 months (OR = 1.14 [95% CI: 0.92–1.42]), after adjusting for confounding factors
- Active [illegible] men was significantly associated with failure to conceive within 6 months, after adjusting for confounding factors including the women's smoking. However, active smoking by men was not associated with failure to conceive within 6 months
- Heavy [illegible] independently associated with delayed conception, and delays lengthened with [illegible] cigarettes smoked

Pregnancy and Pregnancy Outcomes

Epidemiologic Evidence

Smoking Patterns Among Women During Childbearing Years

National data for the United States indicate that somewhere between 13 percent (National Center for Health Statistics, reported in Guyer et al. 1999) and 17 percent (Substance Abuse and Mental Health Services Administration 2001) of pregnant women smoke. For 1998, the 2001 Surgeon General's report gives a figure of 12.9 percent based on birth certificate data (USDHHS 2001). The prevalence of pregnant women who smoked in 2001 was 12 percent, and the prevalence of teenage mothers aged 15 through 19 years who smoked during pregnancy was 17.5 percent in 2001 (Martin et al. 2002). The proportion of women who smoke during pregnancy has declined over the last 10 years; in 1990, 18 percent of women reported prenatal smoking (Guyer et al. 2000). At the same time, smoking among teenage mothers was increasing. In 1994, 16.7 percent of teenage mothers smoked during pregnancy, rising to 17.5 percent in 2001 (Martin et al. 2002). Since somewhere between 18 and 25 percent of women quit smoking once they become pregnant, the proportion of women who smoke around the time of pregnancy is greater than these numbers suggest (Lumley 1987; O'Campo et al. 1995).

Most information on smoking during pregnancy, including that obtained for studies on reproductive effects, comes from self-reports by the pregnant woman. In the United States, smoking during pregnancy is now widely viewed as unacceptable—that is, women are considered responsible for exposing the fetus to tobacco metabolites, and a number of researchers have noted that underreporting of smoking during pregnancy is common. High rates of underreporting have been reported in intervention trials. In a randomized trial from public health maternity clinics, Windsor and colleagues (1993) found a deception rate of 28 percent for self-reports provided at the end of pregnancy using salivary cotinine as a comparison. Underreporting can be a result of the social stigma associated with smoking or the typical change in patterns of smoking during pregnancy. Most women who smoke before pregnancy either quit or reduce their levels of smoking during pregnancy (O'Campo et al. 1995). Thus, if women reduce smoking levels as the pregnancy progresses, they may report the lowest smoking level rather than the greatest, or an average level over the course of their pregnancy. This underreporting, however, is likely to move any positive associations toward a null relationship as this type of misclassification will result in classifying heavy smokers as light smokers and classifying some true smokers as nonsmokers. Researchers have tried to address this problem by incorporating biochemical measures of tobacco exposure into their studies. Three studies showed that cotinine levels in blood collected along with self-reports during the prenatal period were more highly correlated with birth weight than were self-reported smoking levels (Haddow et al. 1987; English et al. 1994; Peacock et al. 1998).

Smoking and Ectopic Pregnancy

Ectopic pregnancy, a rare yet serious complication, occurs when implantation of the fertilized ovum takes place outside of the uterus, often in the fallopian tubes. The etiology of ectopic pregnancy is not fully known but involves the motility and patency of the fallopian tubes. Exposure to nicotine in rhesus monkeys has been shown to decrease tubal motility. Reduced motility may result in the fertilized ovum remaining in the tubes for a longer time which, in turn, may increase the chance of tubal implantation and ectopic pregnancy (Mattison et al. 1989). Cigarette smoking also has been associated with pelvic inflammatory disease, a strong risk factor for tubal pregnancy (Marchbanks et al. 1990). It is unclear whether this association is due to confounding factors such as more sex partners among smokers compared with nonsmokers, or to a direct biologic effect through suppressed immune function in smokers (Holt 1987).

Several studies report an increased risk of ectopic pregnancy among active smokers (Matsunaga and Shiota 1980; Handler et al. 1989; Coste et al. 1991; Kalandidi et al. 1991; Stergachis et al. 1991; Tuomivaara and Romberg 1991) (Table 5.4). ORs for active smokers compared with nonsmokers in these studies ranged from 1.3 to 2.5. Dose-response relationships have been reported in some studies (Handler et al. 1989; Coste et al. 1991) but not others (Phillips et al. 1992). Confounding is a potential source of bias when

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examining maternal smoking and ectopic pregnancy, although most studies adjusted for some potential confounders (e.g., prior problems relating to fertility involving the fallopian tubes or prior infections). The association with smoking does not appear to represent confounding alone.

Smoking and Spontaneous Abortion

Fetal loss or spontaneous abortion is defined as the involuntary termination of an intrauterine pregnancy before 20 weeks of gestation; some studies define spontaneous abortion as occurring before 28 weeks. Spontaneous abortions are extremely difficult to study, as most early fetal losses are underreported and unrecognized. As many as 50 percent of all pregnancies end in miscarriage, and 20 to 40 percent of all pregnancy losses may occur too early to be recognized or confirmed (Wilcox et al. 1988; Eskenazi et al. 1995a). Furthermore, the etiology of spontaneous abortions is multifactorial and not fully understood. Some early miscarriages result from chromosomal abnormalities in the developing embryo; others are related to factors associated with maternal age, the pregnancy, or exposures (e.g., occupational, alcohol consumption, or fever). There is evidence that smoking has a role in promoting spontaneous abortions, and various mechanisms have been proposed. Exposure to nicotine in sea urchins prevents the cortical granule reaction, which eliminates the entry of additional sperm into the egg. If this same process operates in humans, it may be a mechanism by which abnormalities in the developing embryo result in spontaneous abortions (Longo and Anderson 1970; Mattison et al. 1989). Several tobacco components and metabolites are potentially toxic to the developing fetus, including lead, nicotine, cotinine, cyanide, cadmium, carbon monoxide, and polycyclic aromatic hydrocarbons (Lambers and Clark 1996; Werler 1997).

Several studies have reported an increased risk of spontaneous abortion among smokers compared with nonsmokers; the reported ORs range from 1.2 to 3.4 (Kline et al. 1977; Stein et al. 1981; Armstrong et al. 1992; Dominguez-Rojas et al. 1994) (Table 5.5). Various potential confounding factors have been considered in these studies (USDHHS 2001). Dose-response relationships also have been reported (Stein et al. 1981; Armstrong et al. 1992). Armstrong and colleagues (1992) examined three strata of cigarette smoking and compared rates of early fetal loss among smokers and nonsmokers. ORs and CIs for spontaneous abortions for women smoking 1 to 9, 10 to 19, and 20 or more cigarettes compared with nonsmokers were 1.07 (95 percent CI, 0.97–1.18), 1.22 (95 percent CI, 1.13–1.32), and 1.68 (95 percent CI, 1.57–1.79), respectively. Most studies of smoking have not provided an opportunity to explore the basis for a spontaneous abortion. In a study of 2,305 karyotyped cases of miscarriage that separated chromosomally normal from abnormal fetuses, Kline and colleagues (1995) found a higher risk of aborting a chromosomally normal fetus among heavier smokers (>14 cigarettes per day) compared with nonsmokers (*OR = 1.3 [95 percent CI, 1.1–1.7]*). Data from a study of women undergoing IVF indicate that smokers have a higher rate of spontaneous abortions compared with nonsmokers, 42 percent versus 19 percent, respectively (Pattinson et al. 1991).

Some studies have found no association between smoking and spontaneous abortions (Sandahl 1989). In a review of 13 U.S. and European studies, DiFranza and Lew (1995) reported fairly consistent findings across studies despite differences in design, sample selection, and adjustments for confounding. Pooled relative risks (RRs) and ORs were 1.2 (95 percent CI, 1.19–1.3) for cohort studies and 1.32 (95 percent CI, 1.18–1.48) for case-control studies for smokers compared with nonsmokers.

Smoking and Pregnancy Complications

Placenta Previa

Placenta previa occurs when the maturing placenta is close to the cervical os or completely obstructs the os. The etiology of placenta previa is still largely unknown. Some researchers claim that placental enlargement among smokers increases the chance that the placenta implants near or at the cervical os. However, others have found that placentas in smokers and nonsmokers are similar in size, so differences in placental size may be due to factors other than smoking (Zhang and Fried 1992). Zhang and Fried (1992) also note that a detection bias may lead to the greater ascertainment of placenta previa among smokers and will consequently inflate this association in many studies.

Placenta previa consistently has been found to be more frequent in smokers compared with nonsmokers; ORs range from 1.3 to 4.4 with most estimates around 2.3 (Kramer et al. 1991; Williams et al. 1991b; Zhang and Fried 1992; Handler et al. 1994; Chelmow et al. 1996) (Table 5.6). A few studies have examined dose-response associations based on the number of cigarettes smoked per day; one reported a significant dose-dependent relationship (Monica and Lilja 1995)

Table 5.4 Studies on the association between maternal smoking and ectopic pregnancy

Study	Study period	Population	Definition of smoking
Matsunaga and Shinta 1980	January 1962 December 1974	3,611 human embryos derived from artificial termination of pregnancy	Data were not reported
Daling et al. 1987	1979–1981	340 women: 170 with primary infertility and 170 matched controls	Smoking history included number of cigarettes/day, age at smoking initiation, and age at cessation if they had quit
Handler et al. 1989	1983–1987	4,921 women: 634 with ectopic pregnancy, and 4,287 controls who delivered a single live-born infant	• Maternal smoking was recorded as a dichotomous variable (yes/no), and as a continuous variable (number of cigarettes/day) • Four levels of smoking were considered: <10 cigarettes/day, 10–19, 20–29, and ≥30
Coste et al. 1991	During 1988	Women aged 15–44 years attending maternity hospitals	Smo[illegible] classifi[illegible] cigarettes/[illegible] tion [illegible]-ption
Kalantaridou et al. 1991	1986–1987	203 women: 70 with ectopic pregnancy and 133 controls	Ne[illegible] and current smo[illegible]
Stergachis et al. 1991	October 1982–September 1986	1,001 women: 274 who were hospitalized for tubal pregnancy and 727 controls	• N[illegible] cigarettes • Ever smoked • Current and former smokers
Tuomivaara and Ronnberg 1991	1977–1981	929 infertile couples examined and treated for complications	Smoking or not smoking

[a]Pack years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[b]CI = Confidence interval.
[c]Primary infertility due to tubal conditions. The focus of this study is on women with primary infertility (those who have never conceived despite unprotected intercourse for at least one year), diagnosed by the patient's physician and attributed to a tubal condition on the basis of an abnormal hysterosalpingogram or a tubal abnormality identified during surgery.
[d]RR = Relative risk.
[e]OR = Odds ratio.

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Key results
• A number of maternal characteristics including smoking and drinking were significantly associated with either ectopic or myomatous pregnancy • Ectopic pregnancy was significantly associated with lowered parity, previous ectopic pregnancy, and maternal smoking and drinking
• Among current smokers, women who had more than 5 pack-years[a] of exposure had 4.2 (95% CI[b], 1.8–10.2) times the risk of tubal infertility[c] than women who had never smoked • Among women who used ≥6[d] an intrauterine device and smoked, the RR[e] for tubal infertility was 6.7 (95% CI, 1.4–32.5) • There is a possibility that both smoking and tubal infertility are related to factors not addressed in the study, such as exposure to sexually transmitted infections that can cause tubal damage
• Women who reported smoking during pregnancy had a greater than twofold risk of ectopic pregnancy (OR[a] = 2.5 [95% CI, 1.9–3.2]) compared with women who had never smoked • The estimated RR rose from 1.4 (95% CI, 0.8–2.5) for a woman smoking <10 cigarettes/day to 5.0 (95% CI, 2.9–8.7) at ≥30 cigarettes/day • The dose-response relationship supports the argument that smoking may be a causal factor in ectopic pregnancy
• Maternal cigarette smoking was [illegible] ectopic pregnancy (OR = 1.3, 2.48) • The partner's smoking was not [illegible]
• Tobacco smoking significantly increased the risk of an ectopic pregnancy, RR = 2.35 (95% CI, 1.19–3.67)
• The RR of tubal pregnancy associated with ever having smoked cigarettes was 1.3 (95% CI, 1.0–1.8) • Those who smoked at the time of conception had a 40% increase in the risk of tubal pregnancy compared with never smokers (95% CI, 1.0–2.0) • Results support earlier reports of a greater risk of tubal pregnancy associated with current or recent maternal smoking
• Previous ectopic pregnancy, an industrial occupation, and smoking reduced fecundity and increased the risk of ectopic pregnancy • The strongest risk of ectopic pregnancy was associated with a previous tubal pregnancy (9.9-fold risk) • Although current smokers had an increased risk of infertility and ectopic pregnancy, smoking was not a significant indicator in the stepwise logistic analysis, so it could be of secondary importance

Table 5.4 Continued

Study	Study period	Population	Definition of smoking
Phillips et al. 1992	July 1986–April 1987	170 pregnant women: 69 with tubal ectopic pregnancy and 101 controls	• Current smokers (number of cigarettes/day smoked during the month of conception, and the total number of years of smoking) • Not currently smoking • Former smokers (smoked before the month of conception)

while others were only suggestive (Handler et al. 1994; Chelmow et al. 1996). Most recent studies adjusted for potential confounders including age, parity, prior caesarean sections, and prior pregnancy terminations.

Placental Abruption

A placental abruption occurs when the normally implanted placenta prematurely separates from the wall of the uterus, and it is associated with high rates of preterm deliveries, stillbirths, and early infant deaths. The etiology of this rare pregnancy complication is not fully known, but risk factors are trauma, multiple births, uterine tumors, advanced maternal age, hypertensive disorders, history of uterine scarring, and prior history of placental abruption (Ananth et al. 1996). Active smoking during pregnancy results in decreased intervillous placental blood flow (Lambers and Clark 1996). Smoking has been proposed as a link to placental abruptions through vasoconstriction and underperfusion around the site of placental implantation, leading to necrosis and hemorrhage (Lehtovirta and Forss 1978).

Most studies have found an increased risk of placental abruption associated with active smoking during pregnancy (Voigt et al. 1990; Williams et al. 1991a; Raymond and Mills 1993; Spinillo et al. 1994a) (Table 5.7). Studies have reported adjusted ORs ranging from 1.4 to 2.4; some report a dose-response relationship, with risks increasing for heavy smokers compared with light smokers (Ananth et al. 1996).

Preeclampsia and Eclampsia

Preeclampsia is a hypertensive disorder developed during pregnancy with proteinuria and edema. The more severe form, eclampsia, includes one or more seizures and/or coma. Preeclampsia is a severe disorder in pregnancy that is associated with maternal mortality, intrauterine growth retardation (IUGR), and preterm birth. Smoking has been negatively associated with hypertensive disorders during pregnancy, although the underlying mechanism is uncertain (Salafia and Sheverick 1999).

Studies on smoking during pregnancy consistently find reduced rates of preeclampsia among smokers compared with nonsmokers (Marcoux et al. 1989; Eskenazi et al. 1991; Klonoff-Cohen et al. 1993; Spinillo et al. 1994b; Sibai et al. 1995; Cnattingius et al. 1997) (Table 5.8). ORs for smokers range from 0.45 to 0.71. Some studies have reported a dose-response relationship, with the lowest rates of preeclampsia among heavier smokers compared with light smokers and nonsmokers (Marcoux et al. 1989).

Preterm Premature Rupture of Membranes

The rupture of the amniotic sac before the onset of labor is called a premature rupture of membranes (PROM). When PROM occurs before 37 weeks of gestation, it is referred to as preterm PROM. PROM is multifaceted in its etiology, possibly involving multiple steps before the membranes rupture (French and McGregor 1996). Potential determinants of PROM include infections, inflammation, physical stress, disturbance of collagen metabolism, and health behaviors such as nutrition and smoking. Cigarette smoke components may increase the risk of PROM through several mechanisms, including disruption of the cytokine system, impairment of immune function in the reproductive tract, and promotion of inflammatory mechanisms (French and McGregor 1996). It also is possible that impaired nutrition, specifically the reduction of

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Key results

- When current smokers were compared with never smokers and former smokers, the adjusted OR for smoking associated with ectopic pregnancy was 2.4 (95% CI, 1.2–5.1)
- Cigarette smoking may be associated independently with ectopic pregnancy, and smoking cessation before the month of conception may reduce this risk

available nutrients and cellular amino acid uptake, is involved in PROM (French and McGregor 1996). However, confirmation of any one of these pathways from smoking to PROM awaits future studies. It is likely that preterm PROM and non-preterm PROM have somewhat different etiologies (French and McGregor 1996).

Preterm PROM has been studied in relation to smoking during pregnancy (Harger et al. 1990; Williams et al. 1992; Spinillo et al. 1994d), with most studies finding an elevated risk (Table 5.9). Adjusted ORs for smokers range from 1.6 to 2.1, and dose-response relationships of risk with daily smoking levels have been investigated but with mixed results (Williams et al. 1992; Spinillo et al. 1994d). Studies that have shown no increased risk for smokers generally had small sample sizes and inadequate consideration of potential confounding (Harger et al. 1990).

Shortened Gestation

A shortened gestational period can be measured in two ways: by the number of days or weeks of pregnancy and by a preterm delivery, defined as less than 37 weeks of completed gestation. One major mechanism whereby active smoking leads to a shortened gestation is through pregnancy complications. Smoking during pregnancy increases the risk for and exacerbates several pregnancy complications such as PROM, infections, placenta previa, and placental abruption, which in turn are associated with shortened gestations. When a shortened gestation is measured in continuous days, differences between smokers and nonsmokers are on the order of two to three days.

A shortened gestation attributable to smoking, measured by a preterm delivery, has been reported in numerous studies. In a meta-analysis of 20 prospective studies, Shah and Bracken (2000) reported an overall adjusted OR for a preterm delivery of 1.27 (95 percent CI, 1.21–1.33) for smokers compared with nonsmokers. Not all of the 20 studies reported a significantly elevated risk for smokers compared with nonsmokers, and very few accounted for complications such as PROM, infections, placenta previa, or others. Shiono and colleagues (1986b) studied preterm delivery risks for light and heavy smokers, stratifying their sample by the presence of pregnancy complications (PROM, placenta previa, or placental abruption) and no complications. These authors reported that the risk of a preterm delivery was elevated both among the subsamples with complications and within the sample with no pregnancy complications, suggesting that prenatal smoking may act to increase rates of preterm deliveries by causing complications and also by a more direct pathway.

Birth Weight and Intrauterine Growth Retardation

Key outcomes in relation to maternal smoking during pregnancy include birth weight, LBW, and IUGR. Infants with LBW, defined as weighing less than 2,500 g at birth, have a higher risk of subsequent infant morbidity, mortality, and longer-term childhood and adult adverse consequences. IUGR, as the name implies, is reduced fetal physical growth during gestation. One indicator of IUGR, small for gestational age, is often defined as the lowest 10 percent of birth weights (or sometimes the lowest 5 percent) for any gestational age. A number of possible mechanisms leading to reductions in birth weight and fetal growth as a result of smoking have been suggested.

Table 5.5 Studies on the association between maternal smoking and spontaneous abortion

Study	Study period	Population	Definition of smoking
Kline et al. 1977	April 1974–August 1976	894 women aged 18–40 years, who were admitted to public services for spontaneous abortions (574 cases and 320 controls)	• Nonsmokers did not smoke during pregnancy • Smokers smoked during pregnancy (0–19 cigarettes/day or >20 cigarettes/day)
Seidman et al. 1981	6 years	4,088 women: 2,748 with spontaneous abortion and 1,340 controls who carried their pregnancies to 28 weeks or more	• Never smokers • Current smokers • Former smokers
Sandahl 1989	Data were not reported	2,747 pregnant women who consulted a hospital: 610 with spontaneous abortion, 800 with induced abortion, and 1,337 deliveries	Two different definitions of smoking: (1) smokers and nonsmokers, (2) smoked >10 cigarettes/day, and nonsmokers
Armstrong et al. 1992	1982–1984	96,000 women who had a delivery or a spontaneous abortion in a hospital	Number of cigarettes/day
Dominguez-Rojas et al. 1994	January 1989–June 1991	711 female hospital workers aged 20–41 years	• Nonsmokers • Smokers: 1–10 cigarettes/day and >10 cigarettes/day
Kline et al. 1995	1974–1988	6,609 women: 2,376 with spontaneous abortion and 4,233 controls	• Never smoked • Former smokers • Current smokers (1–13 cigarettes/day) • Current smokers (>14 cigarettes/day)

*OR = Odds ratio.

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Key results
• Women who had aborted spontaneously reported smoking during pregnancy more often (OR* = 1.8) than those who delivered after 28 weeks of gestation • Findings suggest that the association between spontaneous abortion and smoking status is lower in women with a history of two or more spontaneous abortions than in women without previous multiple abortions • This trend should be confirmed through independent data before making interpretations
• There was a dose-response relationship between an increased risk of spontaneous abortion and the number of cigarettes smoked • The OR of spontaneous abortion increased by 46% for the first 10 cigarettes smoked and 61% for the first 20 cigarettes smoked • The OR of spontaneous abortion for a woman who smoked 1 pack/day and who drank alcohol daily was 1.08 times more than for an abstinent nonsmoker • Findings suggest that smoking during pregnancy but not before conception is associated with spontaneous abortion
• There was no significant effect of smoking on miscarriage; the only trend was that smokers had a slightly reduced OR for miscarriage • In late miscarriages (week 20 or later), there is a tendency for an OR above 1, but this finding is based on a small number of pregnancies and is not statistically significant
• The OR for spontaneous abortion increased by a factor of 1.2 for each 10 cigarettes/day • Alcohol consumption was not associated with an elevated risk for spontaneous abortion; the OR increased by a factor of 1.26 for each cup/day • The association between coffee and spontaneous abortion was weaker but statistically significant; the OR increased by 1.1 for each cup/day
• Tobacco and caffeine were risk factors for spontaneous abortion • There was a dose response relationship between maternal smoking and spontaneous abortion: the adjusted OR for ≥11 cigarettes/day was 3.55 (95% confidence interval, 1.65–6.32)
• Cigarette smoking during pregnancy was associated with chromosomally normal spontaneous abortions • Both former and current smoking were associated inversely with trisomic loss in women under 30 years of age and positively in older women

Table 5.6 Studies on the association between maternal smoking and placenta previa

Study	Study period	Population	Definition of smoking
Kramer et al. 1991	1984–1987	3,020 singleton births: 598 with placenta previa and 2,422 controls	• Smokers: mothers who smoked at any time during pregnancy • Nonsmokers: mothers who did not smoke at any time during pregnancy
Williams et al. 1991b	August 1977–March 1986	12,433 mothers: 69 with placenta previa and 12,351 controls	• Smokers ever smoked during first or second trimester • Three levels of cigarette smoking: nonsmokers, smokers of 1–9 cigarettes/day, and smokers of ≥10 cigarettes/day • Three levels of smoking duration: nonsmokers, smokers [illegible] and smokers [illegible]
Zhang and Fried 1992	1988–1989	4,646 women from birth certificate data from 1 state: 766 women with placenta previa and 3,880 controls	• Smoking during pregnancy • Average number of cigarettes/day
Handler et al. 1991	1988–1990	3,096 women: 304 with placenta previa and 2,792 controls	• Maternal smoking was recorded as a dichotomous variable and as a [illegible] (number of cigarettes) • Women were classified in smokers and nonsmokers according to the [illegible]
Monica and Lilja 1995	1973–1990	1,825,998 infants from a birth registry	Women were classified by cigarette smoking during pregnancy as nonsmokers, smokers of <10 cigarettes/day, and smokers of ≥10 cigarettes/day
Chelmow et al. 1996	July 1992–March 1994	128 pregnant women: 32 with placenta previa and 96 controls	• Never, former, and present smokers • Light smokers: [illegible] • Heavy smokers: [illegible]

*OR = Odds ratio
†CI = Confidence interval.

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Key results
• Maternal smoking approximately doubled the risk of placenta previa after adjusting for maternal age (OR* = 2.1 [95% CI†, 1.7–2.5]) • The association between maternal smoking and placenta previa did not alter when other confounding variables were adjusted for including marital status, parity, gravidity, previous cesarean section, and both previous spontaneous abortions and elective abortions
• Women who smoked during the first two trimesters of pregnancy had a 90% increase in risk for placenta previa (OR = 1.9 [95% CI, 1.2–3.0]) than women who did not smoke during pregnancy • Compared with never smokers, those who smoked throughout pregnancy had a threefold increase in risk for placenta previa (OR = 3.1 [95% CI, 1.2–8.1]) • The duration of smoking was not an independent risk factor for placenta previa when smoking during pregnancy was considered
• Although maternal smoking during pregnancy might affect placenta previa, the magnitude was substantially smaller than previously reported • After potential confounders such as maternal age, race, gravidity, parity, and previous pregnancy terminations were controlled for, the OR was 1.29 (95% CI, 1.05–1.58) with slight dose-response gradients
• A dose-response relationship between smoking cigarettes and placenta previa was observed independently of other known risk factors • Pregnant women who smoked ≥20 cigarettes/day were more than two times more likely to experience placenta previa compared with nonsmokers (OR = 2.2 [95% CI, 1.6–3.5]) • Pregnant women who used cocaine were 1.4 times (95% CI, 1.8–2.4) as likely to experience placenta previa as nonusers
• Maternal smoking was an independent risk factor for placenta previa. The OR for placenta previa and maternal smoking compared with women without placenta previa was 1.53 (95% CI, 1.4–1.67) for all smokers • The effect of smoking on the risk of having placenta previa increased with increasing parity but did not differ in the maternal age groups • A dose-response relationship between the number of cigarettes/day during pregnancy and the risk of placenta previa was indicated
• Current cigarette smoking was associated with a 2.6- to 4.4-fold increased risk of placenta previa • A dose-response relationship was suggested: compared with never smokers, the OR for light smokers was 2.2 (95% CI, 0.87–7.83) and for heavy smokers 4.0 (95% CI, 0.69–33.1)

Table 5.7 Studies on the association between maternal smoking and placental abruption

Study	Study period	Population	Definition of smoking
Lehtovirta and Forss 1978	NR*	12 healthy women aged 19–31 years, 35–40 weeks pregnant	All participants had smoked cigarettes before but not during pregnancy
Voigt et al. 1990	1984–1986	3,412 s... with abr... 4,225 con...	Smokers smoked at any time during pregnancy
Williams et al. 1991a	1977–1980	1,400 women, 245 with abruptio placentae and 1,257 controls	NR
Raymond and Mills 1993	1974–1977	30,681 singleton pregnancies at ≥28 weeks of gestation	• Smokers or nonsmokers unless otherwise noted • Categorized by packs/day (0, <0.5, 1, ≥1.5) • Heavy smokers (≥1 pack/day)
Spinillo et al. 1994a	1985–1991	781 women, 55 with abruptio placentae, and 726 controls who delivered between 24 and 36 weeks of gestation	• Nonsmokers • Former • <10 cigarettes/day • ≥10 cigarettes/day
Anardi et al. 1998	Ja... 1986–D... 19...	91,667 women seeking antenatal care from hospitals	Smokers had smoked during pregnancy

*NR = Data were not reported.
†RR = Relative risk
‡CI = Confidence interval.
§OR = Odds ratio.

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Key results

- Smoking caused an acute reduction in intervillous blood flow of the human placenta in near-term pregnancy
- Repeated decreases in intervillous blood flow could explain growth retardation of the fetus and other pregnancy-related complications in women who smoke
- A possible effect of nicotine was also seen in accelerated heart rate and elevated blood pressure during smoking

- Smoking was associated with placental abruption (RR[a] = 1.6 [95% CI[b] 1.3–1.8])
- The association with small for gestational age (SGA) status was identical for smokers and nonsmokers
- The increase in SGA infants among women whose pregnancies were complicated by abruption was not explained by maternal smoking

- Lifestyle factors associated with abruptio placentae in univariate analyses include maternal cigarette smoking, marijuana use, and alcohol consumption during pregnancy
- Although the association of cigarette smoking during pregnancy was of borderline significance (OR[c] = 1.5 [95% CI, 1.0–2.2]), the risk of abruption rose with increased levels of smoking

- Each pack of cigarettes smoked/day increased the risk of placental abruption by 40% (OR = 1.39 [95% CI, 1.09–1.79])
- If abruption occurred, the perinatal mortality rate was substantially higher in offspring of women who smoked >1 pack/day than in offspring of nonsmokers (RR = 2.53 [95% CI, 1.14–5.61])
- Heavier smoking increased the risk of abruption and perinatal death

- Abruptio placentae was associated with [illegible] history of antenatal visits, smoking during pregnancy, hypertension, intravenous drug [illegible] history of recent abdominal trauma
- Since abruption is highly associated with [illegible] gestational age and smoking is a primary risk factor for preterm delivery, the increased rate of preterm delivery among smokers may in part account for the correlation between smoking and abruptio placentae

- Smokers had a RR of 2.05 for abruption and 1.56 for placenta previa compared with nonsmokers (RR = 1.0)
- Cigarette smoking was not associated with uterine bleeding of unknown etiology

Table 5.8 Studies on the association between maternal smoking and preeclampsia

Study	Study period	Population	Definition of smoking
Marcoux et al. 1989	1984–1986	928 women: 172 with preeclampsia, 251 with gestational hypertension, and 505 controls	• Never smokers had never smoked • Former smokers stopped smoking at any time before pregnancy • Smokers smoked ≥1 cigarette/day at the beginning of the pregnancy
Eskenazi et al. 1991	1984–1985	371 pregnant women: 139 women with preeclampsia and 132 controls with no hypertensive pregnancy disorder	Smoking habits were classified as yes/no
Klonoff-Cohen et al. 1993	January 1984–December 1986	225 women aged 15–35 years: 110 nulliparous women with preeclampsia and 115 healthy nulliparous women	Smoking was determined by (1) lifetime smoking history (ever smoked/never smoked); and (2) smoking during pregnancy (smoked/did not smoke)
Spinillo et al. 1994b	1990–1992	585 pregnant women who had prenatal care and delivered at a hospital	• Never smoked • Smoked <10 cigarettes/day • Smoked ≥10 cigarettes/day
Sibai et al. 1995	Data were not reported.	2,947 healthy women with a single fetus	• Never smoked or had not smoked for >1 year • Quit at the start of pregnancy • Continued smoking
Cnattingius et al. 1997	1987–1993	317,632 women aged 15–34 years who had had a single birth	• Nonsmokers: nondaily smokers • Moderate smokers: 1–9 cigarettes/day • Heavy smokers: ≥10 cigarettes/day

[a]RR = Relative risk.
[b]CI = Confidence interval.
[c]OR = Odds ratio.

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Key results

- Compared with women who had never smoked, women who were smokers at the onset of pregnancy had a reduced risk of preeclampsia (RR* = 0.51 [95% CI†, 0.34–0.77])
- The protective effect of smoking on preeclampsia was stronger for women who continued to smoke after 20 weeks of pregnancy
- While smoking tended to reduce the risk of gestational hypertension, the effect was less evident than that of preeclampsia

- Smoking was associated with a reduced risk of preeclampsia (adjusted OR† = 0.45 [95% CI, 0.18–1.1]) in both multiparous and nulliparous women
- High body mass, working during pregnancy, and a family history of hypertension were significant risk factors for preeclampsia

- Smoking during pregnancy was not associated with preeclampsia (OR = 0.71 [95% CI, 0.33–1.5]) after adjusting for confounding variables
- There was no evidence of a dose response relationship with a reduced risk for heavy smokers (nonsmokers = 0 packs/day, light smokers = <1/2 pack/day, heavy smokers = >1/2 pack/day)
- To identify dose-response relationships, smokers were divided into the following categories: 0 packs, <1/2 pack/day, and ≥1/2 pack/day; adjusted ORs = 0.65 (95% CI, 0.27–1.55) for light smokers and 0.88 (95% CI, 0.23–3.28) for heavy smokers, compared with nonsmokers; these ORs reflect a slight inverse trend where heavy smokers had a lower reduction in risk than light smokers

- Smoking during pregnancy was a significant protective factor against the occurrence of preeclampsia (adjusted OR = 0.5 [95% CI 0.28–0.8])
- A history of previous abortions, previous pregnancies, low reticulocyte count, low platelet count, and decreased maternal blood volume were risk factors independently associated with the occurrence of preeclampsia
- The study concluded that smoking during pregnancy reduced the risk of preeclampsia; however, the harmful consequences of smoking on pregnancy outcomes far outweigh the risk reduction

- There was a significant inverse relationship between cigarette smoking and preeclampsia when smoking history was dichotomized between current or recent smokers, and those who had never smoked or had quit at least a year earlier
- Findings indicate that cigarette smoking during pregnancy is associated with a reduced incidence of preeclampsia
- The highest incidence of preeclampsia was among women who had never smoked (5.9%), and the lowest incidence was among those who had quit at the start of pregnancy (2.7%)

- Maternal smoking was associated with significantly reduced risks of mild and severe preeclampsia (RR = 0.6 and 0.5, respectively)
- In pregnancies with severe preeclampsia, smoking ≥10 cigarettes/day was associated with increased rates of perinatal mortality (from 24.36 per 1,000), abruptio placentae (from 31.67 per 1,000), and small for gestational age (SGA) infants (from 28.68%)
- Smokers in whom preeclampsia develops have very high risks of perinatal mortality, abruptio placentae, and SGA infants

Table 5.9 Studies on the association between maternal smoking and premature rupture of membranes

Study	Study period	Population	Definition of smoking
Harger et al. 1990	1982–1983	594 women: 341 women with PROM* and 253 controls	• Cigarette smoking only • Nonsmokers • Stopped before pregnancy • Stopped during pregnancy • Current smokers
Williams et al. 1992	August 1977 March 1980	3,067 mothers who delivered at 1 hospital: 307 with PROM, 188 preterm non-PROM mothers, and 2,262 controls	[illegible] of
Spinillo et al. 1994d	1988–1992	405 pregnant women: 138 diagnosed with idiopathic premature membrane rupture and 267 controls	Data were not reported

*PROM = Premature rupture of membranes.
†OR = Odds ratio.

On the basis of animal studies, it appears that nicotine acts on the respiratory and central nervous systems of the fetus and concentrates in maternal and fetal blood, amniotic fluid, and breast milk (Lambers and Clark 1996). The physiologic effects of tobacco on fetal growth may result from the vasoconstrictive effects of nicotine on the uterine and umbilical arteries and an increase in carboxyhemoglobin, leading to reduced oxygenation of the fetus (Lambers and Clark 1996; Werler 1997). Nicotine may have a direct toxic effect on the fetal cardiovascular system resulting in reduced blood flow (Bruner and Forouzan 1991). Abstaining from smoking for 48 hours during the third trimester increased the available oxygen to the fetus by 8 percent (Davies et al. 1979). Cadmium from cigarette smoke accumulates in the placenta and leads to morphologic and functional impairment (Sikorski et al. 1988). The fetus is likely exposed to the cadmium because this element has been detected in cord blood (Chatterjee et al. 1988).

Some researchers have argued against a nutritional effect of smoking on reduced fetal weight and size; smoking mothers have been found to eat more than nonsmoking mothers, and an increased energy intake does not prevent IUGR (Muscati et al. 1996). Furthermore, tricep and subscapular skinfold measurements of infants of smokers were found to be normal and/or similar to those of infants of nonsmoking mothers (Harrison et al. 1983). In fact, infants of smokers lose lean body mass and not adipose tissue, which is consistent with the hypothesis that maternal nutrition is not a mediator of this effect. Hypoxia has been suggested as mediating part of this process (Harrison et al. 1983).

The primary mechanism by which birth weights are reduced among infants of smokers compared with those of nonsmokers is through fetal growth restriction. Birth weight and LBW, however, were often examined for research purposes, as both are available and reliably reported for nearly all infants. Accurate determination of IUGR, however, requires an estimate of the gestational age of the infant, which is subject to greater uncertainty and misreporting.

Reported birth weight differences between infants of smokers and infants of nonsmokers are surprisingly consistent across studies and populations (Simpson 1957; Butler et al. 1972; D'Souza et al. 1981; Sexton and Hebel 1984; Backe 1993; Bardy et al. 1993; Wilcox 1993; Ellard et al. 1996) (Table 5.10). On average, women who smoke throughout their pregnancies

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Key results

- Current smoking, antepartum vaginal bleeding in more than one trimester, and previous preterm delivery were independent risk factors for preterm PROM
- The OR[1] for current smoking was 2.1 (95% CI[2], 1.4–3.1)
- Smoking cessation by pregnant women may reduce the risk of preterm PROM

- The RR[3] of preterm PROM for women who reported ever having smoked during pregnancy compared with nonsmokers was 1.6 (95% CI, 1.1–2.4)
- No gradient between the number of cigarettes/day and the risk of preterm PROM was observed
- Women who smoked during pregnancy had an increased risk of preterm non PROM (adjusted OR = 2.1 [95% CI, 1.4–3.1])

- Previous preterm deliveries, preeclampsia, low social class, maternal smoking, high body mass index, 1st and 2nd–3rd trimester hemorrhages, maternal anemia, and incompetent cervix were significant risk factors for preterm PROM
- Cigarette smoking and reproductive history were significant risk factors for both early (<32 weeks) and late (≥32 weeks) PROM

[1]CI = Confidence interval.
[2]RR = Relative risk.

have infants who weigh about 200 g less than infants of women who do not smoke during pregnancy. Women who quit smoking early in their pregnancy have infants with similar weights to infants of nonsmokers (USDHHS 1990). Thus, the evidence on birth weights after smoking cessation by the mother supports the hypothesis that smoking contributes to lighter infants. Numerous studies also document the association between active smoking during pregnancy and LBW (Hopkins et al. 1990; McDonald et al. 1992; Matnous and Hueston 1994). Only a few studies have not found an association between lower birth weights among smoking compared with nonsmoking mothers, and numerous studies have demonstrated a dose-response relationship with the number of cigarettes smoked and the degree of reduction in birth weights. Studies with biochemically measured smoking exposures (e.g., cotinine levels) also have confirmed, in an even stronger dose-response pattern than that seen from self-reported data, the relationship between prenatal smoking and birth weight (Haddow et al. 1987; Bardy et al. 1993; Li et al. 1993; Eskenazi et al. 1995b; Peacock et al. 1998).

The greatest risk of subsequent mortality and morbidity is among infants born with very low birth weight (VLBW), or weight at birth of less than 1,500 g. VLBW occurs in approximately 3 percent or fewer births; thus, very few studies have a large enough sample size to be able to break out VLBW infants to examine the association with smoking. Hopkins and colleagues (1990) examined the association between smoking and VLBW for births in Ohio for 1989 and reported elevated risks (adjusted OR = 1.4 and population attributable risk = 8.4 percent) among smokers compared with nonsmokers. More recent reviews, however, suggest that the effect of smoking during pregnancy on birth weight is primarily on infants who weigh around 2,500 g and that smoking does not substantially increase the risk of VLBW (Shiono and Behrman 1995; Strobino 1999). Further studies are needed to determine whether and how smoking during pregnancy is related to VLBW births.

The association between smoking and IUGR also has been demonstrated in a number of studies (Chattingius 1989; Ferraz et al. 1990; Wen et al. 1990; McDonald et al. 1992; Backe 1993; Bakketeig et al. 1993; Lieberman et al. 1994; Spinillo et al. 1994c) (Table 5.10).

Table 5.10 Studies on the association between maternal smoking, birth weight, and intrauterine growth retardation

Study	Study period	Population	Definition of smoking
Simpson 1957	1953–1955	7,499 obstetric patients from 3 hospitals	• Nonsmokers did not smoke • Light smokers: 1–10 cigarettes/day • Heavy smokers: >10 cigarettes/day
Butler et al. 1972	March 1958–May 1958	16,094 singleton births occurring [illegible] and 7,000 late [illegible] fetal deaths occurring during the following [illegible]	• Nonsmokers did not smoke • Smokers: four groups based on the average number of cigarettes smoked (1–4, 5–9, 10–15, 20–30)
D'Souza et al. 1981	NR[4]	452 mothers aged 19–35 years, who attended antenatal clinics and had normal singleton pregnancies	• Nonsmokers did not smoke • Light to moderate smokers: 1–14 cigarettes/day • Heavy smokers: ≥15 cigarettes/day
Sexton and Hebel 1984	2½ years	935 women, aged 14–42 years, 463 receiving smoking cessation interventions and 472 controls	Women were classified by the number of cigarettes/day (0, 1–5, 6–10, 11–20, >20)
Martin and Bracken 1986	May 1980–March 1982	3,891 antenatal patients	Tobacco smoke exposure, none, passive (exposed to someone else's cigarette for at least 2 hours/day), direct, and passive and direct
Haddow et al. 1987	July 1980–June 1983	4,211 w[illegible] and 21 weeks of gestation	Smokers were classified by reported daily cigarette use and serum cotinine levels

[3]NR = Data were not reported.
[4]RR = Relative risk.
[5]CI = Confidence interval.

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Key results

- Incidence of premature births was twice as great for smokers as for nonsmokers
- Prematurity rates increased with the number of cigarettes/day; the highest rates were for heavy smokers and the lowest were for nonsmokers

- Mortality rates for late fetal plus neonatal deaths, according to the average number of cigarettes/day, showed that the death rate was lowest for nonsmokers, intermediate for those smoking 1 to 4 cigarettes/day, and highest among those smoking >4 cigarettes/day
- Smoking habits established at the end of the fourth month of pregnancy had an effect on perinatal mortality independent of maternal prepregnancy smoking habits
- Similarly, the effect on birth weight of smoking before pregnancy became nonsignificant after taking into account the average number of cigarettes smoked regularly after the fourth month

- Heavy smokers gained significantly less weight than nonsmokers, but there was no significant difference in skinfold thickness
- Babies born to smokers weighed less, had smaller head circumferences, and were shorter than those born to nonsmokers, but skinfold thickness was similar

- The treatment group infants had a mean birth weight 92 g heavier and were 0.6 cm longer than the control infants
- There were no significant differences between the two groups in head circumferences, gestational age, or Apgar scores
- Findings suggest that some fetal growth retardation can be overcome by smoking cessation assistance to pregnant women

- The ROR[a] of low birth weight for passive exposures to smoke compared with unexposed women was 2.17 (95% CI[b], 1.05–4.5)
- Those passively exposed to smoke delivered infants 24 g lighter on average
- The risk of low birth weight at term attributable to direct cigarette smoking was 3.54 (95% CI, 1.62–7.71)

- Both cotinine levels and smoking history were significantly associated with reduced birth weight, but cotinine correlated significantly better
- Women who smoked >20 cigarettes/day had infants 280 g lighter than nonsmokers
- Women with high cotinine levels (≥ 281 ng/mL) had infants who were 241 g lighter than infants of women with low cotinine levels (≤ 24 ng/mL)

Table 5.10 Continued

Study	Study period	Population	Definition of smoking
Cnattingius 1989	1983–1985	280,809 live births to women aged 15–44 years	• Nonsmokers: nondaily smokers • Moderate smokers: 1–9 cigarettes/day • Heavy smokers: ≥10 cigarettes/day
Alameda County Low Birth Weight Study Group 1990	NR	311 black and 220 white singleton infants of normal birth weight selected randomly	[illegible] smoking during pregnancy: did not smoke [illegible] at the beginning of pregnancy; off and on; and regularly throughout
Ferraz et al. 1990	September 1984–February 1986	3,406 singleton infants: 429 preterm, 422 with intrauterine growth retardation, and 2,555 controls with normal birth weights and gestational ages	NR
Fox et al. 1990	NR	714 children whose mothers smoked at the beginning of pregnancy	• Women [illegible] smoked throughout pregnancy • Quitters [illegible] who reported [illegible] cigarettes/day at the [illegible] birth contact
Hopkins et al. 1990	January 1989–June 1989	74,139 singleton infants: 62,732 white infants and 11,407 black infants	• Light smokers: <0.5 pack/day • Moderate smokers: 0.5–1 pack/day • Heavy smokers: >1 pack/day
Wen et al. 1990	January 1983–January 1988	15,535 births from women who received prenatal care and who delivered at 1 hospital	Cigarette use during the pregnancy before the first visit
McDonald et al. 1992	NR	40,445 single pregnancies from a survey	Women were classified as nonsmokers, smoked <10 cigarettes/day, 10–19 cigarettes/day, or ≥20 cigarettes/day

[a]OR = Odds ratio.
[b]SGA = Small for gestational age.

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Key results
• A significant interaction between maternal age and moderate or heavy smoking was observed for the risk of having a SGA[a] infant • The RR of SGA for heavy smokers vs. nonsmokers was 1.9 in the youngest age group and 3.4 in the oldest age group
• The RR of low birth weight in black smokers compared with black nonsmokers was 3.0; in white smokers it was 3.0 • The RR of term low birth weight (intrauterine growth retardation) was 4.9 in black smokers and 5.1 in white smokers • Quitting smoking in the first 3 months of pregnancy was associated with a lower RR for low birth weight for black and white babies
• Smoking, a heavy workload during pregnancy, <5 or >10 antenatal visits, and any gestational or intrapartum complications were associated with higher risks of preterm and intrauterine growth-retarded births • For preterm cases, the adjusted OR[b] associated with smoking during pregnancy was 1.5 (95% CI, 1.2–2.0) • For intrauterine growth retardation, the adjusted OR for smoking during pregnancy was 1.5 (95% CI, 1.1–2.0)
• By 3 years of age, the children of women who had quit smoking during pregnancy were taller and heavier than those of women who had smoked throughout the pregnancy • Differences in weight but not in height were partly accounted for by the postpartum maternal smoking status • Results suggest that deficits associated with maternal smoking are not overcome by 3 years of age, and some of the observed anthropometric deficits may be extensions of deficits in fetal growth
• Infants born to smokers were more than twice as likely to have low birth weight as infants born to nonsmokers • The risk of low birth weight increased by the level of exposure: adjusted ORs = 1.8, 2.2, and 2.4 for light, moderate, and heavy smokers, respectively • For both blacks and whites, risks were directly proportionate to smoking levels
• Smoking lowered birth weights by decreasing fetal growth and by lowering gestational age at delivery • The effect was significantly greater as maternal age increased; smoking was associated with a fivefold increased risk of growth retardation in women aged >35 years, but less than a twofold risk in women aged <17 years • Smoking reduced birth weights by 134 g in younger women, and by 401 g in women aged >35 years
• The risk of low birth weight for gestational age (LBWGA) increased substantially with smoking: for every 10 cigarettes/day, the risk of LBWGA increased by a factor of 1.51 (95% CI, 1.44–1.57) • Smoking accounted for 39% of LBWGA cases, 35% of low birth weights, and 11% of preterm births • Risk was reduced for women who decreased their smoking and who smoked before but not during the first trimester

Table 5.10 Continued

Study	Study period	Population	Definition of smoking
Werler et al. 1992	1970–1990	2,657 infants from a surveillance program on birth defects: 76 with gastroschisis and 2,581 controls	Smoking was determined by the number of cigarettes/day during pregnancy
Rachel 1992	1988–1989	1,003 women in 1 county who delivered during a 1 year period	The number of cigarettes/day (0, 1–5, 6–10, 11–20, >20)
Bakketeig et al. 1993	January 1986–March 1988	5,422 pregnant women	Smokers: women who at first visit reported daily smoking at the time of conception
Bardy et al. 1993	February 1990–March 1991	1,237 pregnancies and newborns, representing all live birth pregnancies during 1 week in 1 country	• Nonsmokers: had not smoked • Quitters: smoked during the first trimester and then quit • Smokers: smoked during the entire pregnancy
Cnattingius et al. 1993	1983–1988	538,829 women with singleton births	• Nonsmokers: nondaily smokers • Smokers: 1–9 cigarettes/day and ≥10 cigarettes/day
Li et al. 1993	1988–1991	1,277 women <32 weeks pregnant at the first prenatal visit to a clinic	Smokers: at their first prenatal visit reported at least one puff from a cigarette in the last 7 days and/or had a baseline or follow-up cotinine level of ≥30 ng/ml
Wilcox 1993	1980–1984	260,000 white singleton births in 1 state	• Nonsmokers: mothers who reported no smoking during pregnancy • Smokers: mothers who reported smoking ≥1 pack of cigarettes/day • Smokers of <1 pack were excluded

[a]SGA = Small for gestational age.

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Key results
• Cigarette smoking was not associated with gastroschisis • Age-adjusted RRs for smoking and coffee intake were close to 1.0 • There was a strong inverse relationship between maternal age and gastroschisis, with a 16-fold increased risk for the youngest mothers
• Smokers experienced a mean birth weight impairment of 182 g (adjusted for parity and age) • There was a dose-response effect of the number of cigarettes/day on birth weight at the first visit • The RR for SGA[a] newborns of smokers ≤25 years of age was not significant, while women aged ≥26 years had a RR of 2.8
• Mothers who smoked cigarettes around the time of conception nearly doubled their risk of SGA births • If the mother smoked and had a previous low birth weight delivery, the RR rose to nearly 5× • Low prepregnancy weight and smoking together increased the risk of a SGA birth fourfold
• Tobacco exposure was associated with shorter gestational age, reduced birth weight, and shorter crown-heel length of newborns; exposed newborns were on average 188 g lighter and 10 mm shorter than unexposed newborns • Maternal cotinine concentrations explained these dose-related findings better than the reported smoking habits • There was a quantitative dose-response relationship with tobacco exposure, and a decrease in gestational age at birth and in the size of the neonate
• Among multiparous women, smoking increased the ORs for low birth weight and preterm delivery by 2.4 and 1.6, respectively; the corresponding increases for nulliparous women were 1.7 and 1.1, respectively • With advancing maternal age, there was a smoking-related relative increase in the ORs for SGA births • The age effect on the relative increase of low birth weight, preterm delivery, and SGA births was greater among nulliparous women than among multiparous women
• Infants born to women who had quit smoking had the highest mean birth weight, followed by infants born to women who had reduced their smoking, and women who did not change their smoking behavior • Although smoking cessation increased infant gestational age at delivery by 1 week, reducing smoking had no effect • Cotinine values and smoking reduction rates were positively associated with an increase in infant birth weight
• Infants of mothers who smoked ≥1 pack of cigarettes/day were on average 320 g lighter than unexposed infants (3,180 g compared with 3,500 g) • Perinatal mortality for infants of smokers was 14.5 per 1,000 compared with 10.4 per 1,000 for infants of nonsmokers • The RR was not uniform across birth weights: among infants less than 3 kg, weight-specific mortality rates were lower for exposed vs. unexposed infants, among heavier infants, the risk was reversed, with mortality higher for exposed infants • When standardized weight-specific mortality rates are compared, the pattern becomes more consistent, with exposed infants showing a higher risk of mortality across all relative birth weights

Table 5.10 Continued

Study	Study period	Population	Definition of smoking
Lieberman et al. 1994	August 1977–March 1980	11,177 women with singleton pregnancies from a hospital-based cohort	Women were classified as nonsmokers, smoked throughout pregnancy, smoked during the first trimester only, smoked during the first and second trimesters only, and smoked during the second and third trimesters or during the third trimester only
Marcoux and Hueston 1994	1988	4,876 women who gave birth	• Nonsmokers did not smoke cigarettes at all during the year before birth • Smokers: (1) those who stopped [illegible] during the first [illegible] of pregnancy, (2) those who continued smoking beyond the first trimester of pregnancy
Spinillo et al. 1994c	1988–1992	1,041 pregnancies: 347 with fetal growth retardation and 694 controls	Maternal smoking was classified as none, 1–10 cigarettes/day, 11–20 cigarettes/day, and >20 cigarettes/day
Eskenazi et al. 1995	1964–1967	3,529 pregnant women around 27 weeks of gestation	• Smokers: current smokers at the time of interview • Nonsmokers: never smoked or had quit before the pregnancy

[a]SGA = Small for gestational age.

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Key results
• Women who began smoking during the second or third trimester had an elevated risk of SGA[a] births (OR = 1.83 [95% CI, 1.25–2.67]) similar to that of women who had smoked throughout pregnancy (OR = 2.2 [95% CI, 1.9–2.54])
• Risks for SGA births increased with the number of cigarettes smoked during the third trimester
• Women who did not smoke during pregnancy were less likely to give birth prematurely (6.9 vs. 8.2%) or to give birth to a low birth weight baby (5.5 vs. 8.9%) than women who smoked at some time during the year before birth
• Compared with those who smoked beyond the first trimester, those who quit smoking within the first trimester had reductions in the proportion of preterm deliveries (6.7 vs. 9.1%) and low birth weight infants (7.9 vs. 9.6%)
• Fetal growth retardation was associated with maternal smoking (OR = 2.87 [95% CI, 2.17–3.8])
• Smoking-related risks of fetal growth retardation were increased in the case of a male fetus, nulliparity, maternal age <20 years, a history of first trimester hemorrhage, and low prepregnancy weight
• Compared with infants of unexposed nonsmokers, infants of exposed nonsmokers weighed 45 g less on average
• Infants of smokers weighed on average 78, 191, and 233 g less for the first, second, and third cotinine tertiles, respectively
• Birth weight decreased 1 g for every increase in nanomoles per milliliter of cotinine

Table 5.10 Continued

Study	Study period	Population	Definition of smoking
Ellard et al. 1996	NR	3,038 mothers who gave birth to live singleton babies after 28 weeks of gestation	• Smoking was determined by self-reported daily cigarette use (0, 1–12, >12), and urinary nicotine metabolites/creatinine ratios (0, 0.01–11.0, >11.0 µg/mg) • Proven nonsmokers: reported nonsmoking status was confirmed by negative urine tests • Proven smokers: reported smoking was confirmed by positive urine test results
Muscati et al. 1996	1979–1989	1,339 pregnant women	• Nonsmokers: did not report smoking at any time during pregnancy, or had stopped by 10 weeks of pregnancy • Smokers: ≥1 cigarette/day throughout entire pregnancy
Peacock et al. 1998	August 1982–March 1984	1,254 white women seeking antenatal care from a hospital	Number of cigarettes/day

[a]SGA = Small for gestational age.

The RRs range from 1.5 to 2.5 for smokers compared with nonsmokers. Several studies demonstrated dose-response relationships of risk with the amount smoked, with the highest smoking categories showing RRs of 5.0 to 9.9 (Wen et al. 1990; Bakketeig et al. 1993; Lieberman et al. 1994; Spinillo et al. 1994c). Most studies adjusted for numerous potential confounding factors and still reported strong associations and dose-response relationships with daily smoking levels. These associations with active smoking by the mother may be underestimated as a substantial proportion of women in the nonsmoking control groups are exposed to secondhand cigarette smoke. Exposure to secondhand smoke also reduces birth weight, and removing the group of passively exposed women from the control group increases RRs (Martin and Bracken 1986). One study examining the contributions of smoking, energy intake, weight gain, and fetal growth reported that the effect of smoking was independent of energy intake (which was higher in smokers) and weight gain (which was lower in smokers) (Muscati et al. 1996). Thus, this finding supports a direct effect of smoking

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Key results

- Adjusted birth weight deficits of babies born to active smokers averaged 226 g (95% CI, 194–258 g)
- Dose-dependent effects were only apparent when nicotine intake was based on urinary nicotine metabolites/creatinine ratios than on self-reports
- Maternal weight gain during pregnancy was substantially reduced in smokers
- Placental weight gain was unaffected by smoking

- Smoking was [illegible] related with a higher energy intake but a lower maternal weight gain [illegible] (-209 g)
- The important [illegible] smoking on fetal growth retardation cannot be adequately mitigated by simply increasing energy intake
- The estimated percentage of SGA infants attributable to smoking was 30.8%

- Among smokers, cotinine levels were more closely related to birth weight than the number of cigarettes smoked, indicating that cotinine is a better predictor of birth weight than the reported number of cigarettes smoked
- Among nonsmokers, the association between cotinine levels and birth weight was not statistically significant after adjusting for confounding factors
- The difference in mean birth weights between nonsmokers in the lower and upper quintiles of cotinine was 0.2%
- Any effect of maternal passive smoking was small compared with the effects of maternal active smoking on birth weight

on the growth of the fetus rather than an indirect effect through nutritional intake among smokers.

Evidence Synthesis

The evidence addresses smoking during pregnancy and diverse outcomes. For some of the outcomes, causal conclusions have been previously reached. Most studies on the relationship between smoking and ectopic pregnancy have demonstrated a positive association, with several demonstrating a dose-response relationship between risk and amount smoked. However, the number of studies is still limited, and uncontrolled confounding remains as an alternative explanation to a causal association. Biologic mechanisms include a possible indirect causal pathway through an increased risk for a pelvic infection in smokers, a delayed fertilization process, and reduced tubal motility in association with exposures to nicotine.

Despite methodologic challenges in studying spontaneous abortions, most studies on the association between active smoking and spontaneous pregnancy loss have reported increased risks for smokers compared with nonsmokers, and some studies demonstrate dose-response relationships. Animal models have indicated plausible mechanisms that may underlie the association.

Most studies demonstrate an increased risk for maternal smoking and preterm PROM, placenta previa, and placental abruption. These findings have been consistently observed across time and across many study populations in multiple countries. Also, biologic evidence supports the contribution of active smoking to these particular pregnancy conditions.

Many studies show an increased risk of preterm delivery among smokers compared with nonsmokers even though the overall risk of preterm delivery may be small, with ORs on the order of 1.2 or 1.3. One major mechanism by which smoking is related to preterm delivery is through an increase in the risks of pregnancy and/or fetal complications that result in a spontaneous abortion or a medically indicated early delivery.

Many studies have consistently demonstrated a positive association between maternal smoking during pregnancy and reduced birth weight, and several have demonstrated dose-response relationships with the amount smoked. For smoking throughout pregnancy the effect is large, and successful cessation of smoking before the third trimester eliminates much of the reduction caused by maternal smoking. Some mechanisms by which smoking reduces birth weight have been established. They act in large part through reduced fetal growth, but the association between smoking and birth weight also results from early delivery, often from pregnancy complications. The biologic evidence supporting this causal effect is strong and includes fetal hypoxia from increased carboxyhemoglobin; reduced blood flow to the uterus, placenta, and fetus; and direct effects of nicotine and other compounds in tobacco smoke on the placenta and fetus.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy.

2. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and spontaneous abortion.

3. The evidence is sufficient to infer a causal relationship between maternal active smoking and premature rupture of the membranes, placenta previa, and placental abruption.

4. The evidence is sufficient to infer a causal relationship between maternal active smoking and a reduced risk for preeclampsia.

5. The evidence is sufficient to infer a causal relationship between maternal active smoking and preterm delivery and shortened gestation.

6. The evidence is sufficient to infer a causal relationship between maternal active smoking and fetal growth restriction and low birth weight.

Implications

The evidence reviewed in this chapter suggests that smoking is associated with ectopic pregnancy and spontaneous abortion. As both ectopic pregnancy and infertility are on the rise, reducing smoking among women intending to become pregnant is warranted. More studies are needed that are designed to prospectively assess very early losses and to examine the association of smoking around the time of conception with types of spontaneous abortions.

The evidence of an association of smoking during pregnancy and adverse pregnancy complications, such as preterm PROM, placenta previa, and placental abruption, is sufficient to warrant promoting smoking cessation among women before they become pregnant and during pregnancy. Werler (1997) noted that as much as 10 percent of abnormal placentation could be avoided if smoking during pregnancy were eliminated. The decreased risk of preeclampsia among smokers compared with nonsmokers does not outweigh the adverse outcomes that can result from prenatal smoking.

The occurrence of LBW could be reduced by an estimated 20 percent, and fetal growth restriction by 30 percent, if all women were nonsmokers during pregnancy (Alameda County Low Birth Weight Study Group 1990; Cnattingius et al. 1993; Li et al. 1993; Muscati et al. 1996). The impact of smoking on these outcomes can be lessened if women quit before their third trimester; thus, there is a need for widespread implementation of effective smoking cessation interventions targeting all women of childbearing age as well as those already pregnant.

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Congenital Malformations, Infant Mortality, and Child Physical and Cognitive Development

Epidemiologic Evidence

Congenital Malformations

Because of the direct fetal effects observed from exposure to tobacco smoke, and the chemically complex nature of cigarette smoke, researchers have assessed the association between prenatal exposure and congenital malformations. Researchers have examined these associations with malformations as an overall group and with single malformations separately. The etiologies of the multiple congenital malformations vary widely, making the discussion of the contribution of prenatal smoking to an increased risk of birth defects difficult overall.

Most studies investigating associations between maternal smoking during pregnancy and all congenital malformations together have not found an association (Hemminki et al. 1983; Shiono et al. 1986b; Malloy et al. 1989; Seidman et al. 1990; Van den Eeden et al. 1990) (Table 5.11). One study reported an increased risk only among heavy smokers (Kelsey et al. 1978), with an adjusted RR of 1.6 ($p = 0.03$) for women smoking 21 or more cigarettes per day during pregnancy compared with nonsmokers.

Down syndrome has been consistently shown not to be associated with maternal smoking in pregnancy (Hook and Cross 1985; Cuckle et al. 1990a; Van den Eeden et al. 1990; Källén 1997a). Neural tube defects are not elevated among smokers compared with nonsmokers (Malloy et al. 1989; Wasserman et al. 1996; Källén 1998). However, Källén (1998) demonstrated a significant protective effect for neural tube defects among smokers compared with nonsmokers in the 1.2 million births studied (OR = 0.75 [95 percent CI, 0.61–0.91]).

Li and colleagues (1996) reported an association between maternal smoking and urinary tract anomalies among light smokers (<1,000 cigarettes smoked during pregnancy) compared with nonsmokers; the anomalies occurred mainly in female infants. The OR for light smokers versus nonsmokers was 3.7 (95 percent CI, 1.7–8.6); among mothers of female infants, comparing light smokers with nonsmokers yielded an OR of 6.1 (95 percent CI, 2.0–18.4). This study reported a lower risk for heavy smokers compared with nonsmokers (OR = 1.4 [95 percent CI, 0.6–3.3]). As an explanation for this dose-dependent response, Li and colleagues (1996) suggest that heavier smokers may be more likely than light smokers to abort malformed fetuses. Malloy and colleagues (1989) and McDonald and colleagues (1992) found little association between smoking and genitourinary defects at birth.

Gastroschisis is a defect of the abdominal wall closely related to the defect omphalocele thought to result from vascular interruption (Hoyme et al. 1983). Findings on the association between gastroschisis and smoking have been conflicting. Smaller studies show a positive association (Haddow et al. 1993), whereas most larger studies and those controlling for confounders show no association (Werler et al. 1992; Torfs et al. 1994).

The association of fetal limb defects and smoking also has been studied. One study looked at the risk of limb defects from maternal and paternal smoking and found contradictory results (Wasserman et al. 1996). Risk was elevated only with heavy paternal smoking (OR = 2.0 [95 percent CI, 1.3–3.6]) compared with neither parent smoking. Maternal smoking, even heavy maternal smoking, did not elevate the risk of limb defects; nor did having both parents smoke or having passive exposures at home or at work. Because there is no evident biologic explanation for this particular pattern of association, paternal smoking in the absence of maternal smoking may be a proxy for other factors contributing to this risk. This study also reported that the risk of conotruncal heart defects was elevated when both parents smoked (OR = 1.9 [95 percent CI, 1.2–3.1]) (Wasserman et al. 1996).

The most convincing evidence supports an association between smoking and oral clefts (Saxen 1974; Khoury et al. 1987; Hwang et al. 1995; Shaw et al. 1996; Källén 1997b; Wyszynski et al. 1997), yet not all studies report an association (Shiono et al. 1986a; Malloy et al. 1989; Werler et al. 1990). Studies have examined the association with smoking for all oral cleft defects and for the categories of a cleft lip with or without a cleft palate, and cleft palate alone. Even when subgroups are examined, studies produce contradictory findings. One meta-analysis of 11 studies of oral clefts that compared mothers who smoked during the first trimester with mothers who did not smoke reported an overall OR of 1.29 (95 percent CI, 1.18–1.42) for a

Table 5.11 Studies on the association between maternal smoking and congenital malformations

Study	Study period	Population	Definition of smoking
Saxen 1974	1967–1971	599 cases of oral clefts reported to a register of congenital malformations	Smoking during pregnancy: >5 cigarettes/day
Kelsey et al. 1978	1974–1976	4,358 infants: 1,379 with congenital malformations and 2,968 normal controls	The number of cigarettes/day during pregnancy
Hemminki et al. 1983	1967–1977	3,300 children from a register of congenital malformations	• Smoking habits were described in 10 categories in the questionnaire • Different categories of smokers were created separately for the analysis
Hook and Cross 1985[b]	1960–1981	360 mothers: [illegible] Down syndrome [illegible] 130 with child [illegible] other defects, and 10 [illegible] children with [illegible]	• Nonsmokers (those who never smoked) • Former smokers at the time of conception • Current smokers
Shiono et al. 1986a	1974–1977 (birth defects study) 1959–1966 (perinatal study)	33,434 live births in a birth defects study, and 53,512 live births in a perinatal project	The number of cigarettes or packs/day
Khoury et al. 1987	1987	251 [illegible] defe[illegible] 27 w[illegible] cleft[illegible] othe[illegible]	Asking [illegible] smoke [illegible] preg[illegible] nancy [illegible] cigarettes/day (1–9, 10–19, 11–20, >20)
Malloy et al. 1989	1980–1983	288,067 singleton births recorded in birth defects registry	• Nonsmokers: did not smoke • Smokers: <1 pack/day or ≥1 pack/day

[a]RR = Relative risk.
[b]CI = Confidence interval.
[c]OR = Odds ratio.

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Source: https://www.industrydocuments.ucsf.edu/docs/zkmj0001

Key results
• Smoking during pregnancy was significantly more frequent among mothers of children with clefts than among controls • Other factors associated with oral clefts in children included parental age, socioeconomic status, threatened abortion (bleeding and/or pains during pregnancy), pelvic x-ray examinations before pregnancy, emotional factors, and birth weight
• Wo[illegible] smoked >20 cigarettes/day [illegible] and a RR* of about 1.6 for congenital malformations [illegible] scarring compared with wo[illegible] 0 cigarettes/day during pregnancy • Ther[illegible] significant increase in risk in [illegible] reported smoking ≤20 cigarettes/day com[illegible] h women who did not smoke during pregnancy • The [illegible] k in heavy smokers could be a result of confounding factors or response bias, so further rese[illegible] ded to determine a causal relationship between maternal smoking and congenital malfor mations
• The associations between maternal smoking and congenital malformations were statistically nonsignificant. there was a slight increase with the number of cigarettes smoked, suggesting a minor effect • Women who smoked >10 cigarettes/day had a higher frequency of spontaneous abortions than any other group of women
• The [illegible] were stat[illegible] [illegible] exception with Down syndrome was 0.58 [illegible] [illegible] ase defect[illegible] [illegible] e (CI, 0.33–0.95) in the case normal cont[illegible] • The [illegible] ssociation may be attributable to a selective effect of smoking on survival, on the ferti[illegible] of ≤21 gametes before conception, or on survival of ≤21 conceptuses after fertilization
• Since associations found in a single study could be the result of chance, deficiencies in study design, or peculiarities of the population studied, data from another study were used to check for consistencies of the associations initially found • The associations of specific congenital malformations with smoking during pregnancy were suggested in the birth defects study, but the results could not be confirmed by the results from the perinatal study • Smoking is unlikely to be responsible for a large increase in malformations at birth
• Mothers of infants with oral clefts smoked more during pregnancy than mothers of infants with other defects • The OR for cleft lip with or without cleft palate was 2.56, and the OR for cleft palate was 2.39 • There was a dose-response relationship between the daily amount smoked and the risk of clefting
• Infants of women who smoked were not at a greater risk for congenital malformations than infants of women who did not smoke • Maternal smoking appears to be a risk factor for gastrointestinal malformations, but other congenital malformations occur less frequently in infants of smokers compared with nonsmokers

Table 5.11 Continued

Study	Study period	Population	Definition of smoking
Cuckle et al. 1990a,b	NR*	462 pregnant women	• Smoking was determined by cotinine concentrations in maternal serum samples • Maximum likelihood analysis was used to determine cotinine cut-off levels for separating smokers from nonsmokers
Van den Eeden et al. 1992	1984–1986	7,384 mothers with singleton live births: 3,284 with a congenital malformation and 4,500 controls without malformations	NR
Haddow et al. 1993	January 1980–April 1989	62,103 consecutive second trimester singleton pregnancies	Smokers or nonsmokers
Torfs et al. 1994	March 1988–August 1992	320 mothers: 110 mothers of infants with gastroschisis and 220 age-matched mothers of normal infants	≤1 pack/day and >1 pack/day
Hwang et al. 1995	1984–1992	467 infants: 69 with cleft palate, 114 with cleft lip with or without cleft palate, and 284 controls with noncleft birth defects	Records on whether and how many cigarettes were smoked during pregnancy
Li et al. 1996	1990–1991	487 infants: 118 cases and 369 controls	Light smokers, 1–1,095 cigarettes during pregnancy

*NR = Data were not reported.

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Source: https://www.industrydocuments.ucsf.edu/docs/zkmj0001

Key results
• In pregnancies with and without Down syndrome, the 25th, median, and 75th centiles of AFP (alpha-feto protein) and DHEAS (dehydroepiandrosterone) were higher in smokers than in nonsmokers, whereas those for uE_3 (unconjugated estriol), hCG (human chorionic gonadotrophin), and progesterone were lower
• When screening for Down syndrome using maternal age, AFP, uE_3, and hCG, allowance could be made for smoking by deriving separate medians for smokers and nonsmokers to calculate MoM values (multiple of the median value in unaffected pregnancies of the same gestation)
• When all malformations were considered together, there was no association with maternal smoking
• Maternal smoking was associated with increased risks for a number of specific malformations, including [illegible] (RR = 2.0 [95% CI, 1.0–4.0]), cleft defects (RR = 1.4 [95% CI, 1.0–2.0]), and clubfoot (RR = 1.4 [95% CI, 1.0–2.0])
• No association was found with Down syndrome or any other malformation
• Pregnant women who smoked cigarettes had a 2.1 times greater odds of having an infant with gastroschisis than nonsmokers (95% CI, 0.9–4.8)
• Smoking data from this study combined with smoking data from two other studies showed an OR of 1.6 (95% CI, 1.2–2.2)
• There was a significant association of gastroschisis with a history of [illegible] smoking and with the use of either a recreational drug or tobacco during the trimester prior to [illegible]
• During the [illegible] trimester, the OR for the risk of having an infant with gastroschisis for smokers of <1 [illegible] 4 (95% CI, 0.78–2.5) and 1.77 (95% CI, 0.[illegible]) for those of ≥1 pack/day
• A gene-environment interaction between infant genotype and maternal smoking was associated with birth defects among those with or without a family history of birth defects
• Infants carrying the C2 allele who were exposed to maternal smoking of ≥10 cigarettes/day showed a 6.16-fold increase in risks for cleft palate only (95% CI, 1.03–34.7), while similar infants whose mothers smoked ≥10 cigarettes/day showed an 8.69-fold higher risk (95% CI, 1.57–47.8)
• Maternal smoking during pregnancy was associated with a twofold increased risk of congenital urinary tract anomalies in the offspring
• The risk was higher among light smokers (OR = 3.7 [95% CI, 1.7–8.6]) than among heavy smokers (OR = [illegible] 3)
• The [illegible] genital urinary tract anomalies associated with light smoking but not with heavy [illegible] are apparent among female than male offspring

Table 5.11 Continued

Study	Study period	Population	Definition of smoking
Shaw et al. 1996	January 1987–December 1989	1,465 infants: 731 with orofacial clefts and 734 nonmalformed controls	• Active smoking: number of cigarettes/day by the mother during the 4 months after date of conception • Passive smoking: whether anyone else inside the mother's home smoked daily during the 4 months after conception, or whether she regularly frequented places where others smoked • Paternal smoking was determined by how many cigarettes the infant's natural father smoked during the 3 months before through 3 months after conception
Wasserman et al. 1996	1987–1988	1,150 infants: 207 with conotruncal heart defects, 264 with neural tube defects, 178 with limb deficiencies, and 481 controls	• Active smoking: number of cigarettes/day by the mother during the 4 [illegible] after date of conception • Passive smoking: whether anyone [illegible] inside the mother's home [illegible] daily during the 4 months after conception, or whether she [illegible] regularly frequented [illegible] others smoked • Paternal [illegible] determined by how many cigarettes the [illegible] natural father smoked during the 3 months before through 3 months after conception
Källén 1997a	1985–1993	1,321 infants with Down syndrome	• None • <10 cigarettes/day • ≥10 cigarettes/day
Källén 1997b	1982–1992	1,834 infants with oral clefts selected from a birth registry and a congenital malformation registry	• None • <10 cigarettes/day • ≥10 cigarettes/day

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Key results
• The risks associated with maternal smoking were most elevated for isolated cleft lip with or without cleft palate (OR = 2.1 [95% CI, 1.3–3.6]) and for isolated cleft palate (OR = 2.2 [95% CI, 1.1–4.5]) when mothers smoked >20 cigarettes/day
• Clefting risks were even greater for infants with the transforming growth factor alpha (TGF-α) allele whose mothers smoked >20 cigarettes/day
• Risk of orofacial clefting in infants may be influenced by maternal smoke exposure alone, as well as in combination with the presence of the uncommon TGF-α allele (gene-environment interaction)
• Paternal smoking was not associated with clefting, and passive exposures were associated with a slightly increased risk
• Moderately ob[illegible] for conotruncal heart defects (OR = 1.9 [95% CI, 1.24–3.1]) and limb deficie[illegible].9]) with both parents smoking
• There were no [illegible]al abnormalities associated with maternal smoking in the absence of pare[illegible] increased risk associated with paternal smoking in the absence of maternal sm[illegible] limb deficiencies
• Risks associated with paternal smoking for conotruncal defects differed among racial and ethnic groups
• No association between maternal smoking and all cases of Down syndrome was found (OR = 0.98 [95% CI, 0.86–1.11]), but heterogeneity over strata existed
• A decreased OR (0.91 [95% CI, 0.72–1.15]) for any maternal smoking was indicated among primiparous women but not among multiparous women
• Findings indicate that no direct effect of smoking on Down syndrome risk exists, but the association observed in primiparous women is attributable to covarying factors
• A statistically significant association between maternal smoking during [illegible]ral clefts was found
• The OR for maternal smoking among cases of cleft lip with or without a cleft palate was 1.16 (99% CI, 1.02–1.29)
• For cases of cleft palate alone, the OR was 1.29 (99% CI, 1.08–1.54)

Table 5.11 Continued

Study	Study period	Population	Definition of smoking
Wyszynski et al. 1997	1966–1996	Meta-analysis of 11 studies	NR
Kallen 1998	1963–1993	821 infants with neural tube defects	• None • ≤10 cigarettes/day • >10 cigarettes/day

cleft lip with or without a cleft palate, and 1.32 (1.10–1.62) for a cleft palate (Wyszynski et al. 1997). Recent studies have examined genetic and environmental interactions in relation to oral clefts. Two studies (Hwang et al. 1995; Shaw et al. 1996) reported that infants who were heterozygous or homozygous for transforming growth factor alpha allele and were exposed to smoking during pregnancy had significantly increased risks for a cleft palate of 7.0 (95 percent CI, 1.18–28) (Hwang et al. 1995) and 4.0 (95 percent CI, 1.7–9.2) (Shaw et al. 1996). Risks for a cleft lip with or without a cleft palate were lower, about twofold, and were only significant in one study where smoking alone significantly elevated the risks of both outcomes (OR = 1.6) (Shaw et al. 1996). In the other study, smoking alone was not associated with either category of oral clefts (Hwang et al. 1995).

Infant Mortality and Stillbirths

Stillbirths (fetal death after 28 weeks) and infant deaths (death within the first year of life) have been examined in relation to smoking in numerous studies. These outcomes have declined significantly in the United States in recent years, as infant mortality has declined from 13 deaths per 1,000 births in 1980 to 7 deaths per 1,000 in 1998 (Guyer et al. 1999). Much of this improvement before and after 1980 has been from advances in medical interventions for the very smallest and sickest infants. Numerous studies have demonstrated associations between active maternal smoking and stillbirths (Meyer and Tonascia 1977; Kiely et al. 1986; Cnattingius 1992; Little and Weinberg 1993; Raymond et al. 1994) and neonatal and perinatal mortality (Comstock and Lundin 1967; Rush and Kass 1972; Cnattingius et al. 1988; Malloy et al. 1988; Schramm 1997). Even in the face of modern neonatal intensive care, numerous studies have demonstrated increased risks for neonatal mortality (death of a live-born infant within 28 days) (Cnattingius et al. 1988; Malloy et al. 1988; Schramm 1997), with reported ORs for infants of smokers around 1.2 compared with infants of nonsmokers.

SIDS—or sudden, unexplained, unexpected death before one year of age—has been investigated in relation to fetal exposures to maternal smoking and the exposure of the infant to smoking by the mother and others during the postpartum period. Although social and behavioral risk factors for SIDS have been identified, the biologic mechanism is still unknown. Concerning smoking and SIDS, one proposed mechanism is chronic hypoxia—via elevated levels of carbon monoxide or reduced placental perfusion—affecting factors such as the normal development of the central nervous system (Bulterys et al. 1990). In animal studies designed to investigate neurotoxic effects, nicotine was found to target neurotransmitter receptors in the fetal brain, leading to reduced cell proliferation and, consequently, altered synaptic activity. The cholinergic and catecholaminergic systems and neurotransmitter pathways are affected acutely and, possibly, over the long term. Alterations in the peripheral autonomic pathways may lead to increased susceptibility to hypoxia-induced brain damage and SIDS (Slotkin 1998). In a study of newborns, the auditory arousal threshold for babies whose mothers smoked during pregnancy was greater than for those whose mothers did not smoke (Franco et al. 1999). Stick and colleagues (1996) observed the respiratory function of newborns in the hospital and reported lower function in infants of smokers compared with nonsmokers. This observation suggests a fetal effect of smoking that continues beyond the postpartum period.

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Key results

- There was a small increased risk among mothers who smoked during the first trimester of the pregnancy of having a child with either a cleft lip with or without a cleft palate (OR = 1.29 [95% CI, 1.18–1.42]), or with a cleft palate alone (OR = 1.32 [95% CI, 1.10–1.62])
- A highly significant effect of maternal smoking on the incidence of neural tube defects was found (adjusted OR = 0.75 [95% CI, 0.61–0.91])
- A positive dose-response effect of smoking was indicated but was not statistically significant

The death rate attributable to SIDS has declined by more than half over the last two decades; the SIDS rate in 1979 was 151.1 per 100,000 live births, and in 1998 the rate was 64 per 100,000 live births (Guyer et al. 1999). SIDS has decreased dramatically because of interventions such as the "Back to Sleep" campaign implemented in the 1990s. The diagnosis of SIDS, preferably by conducting an autopsy to exclude other causes, makes it a difficult outcome to study. Moreover, studies that examine maternal smoking during pregnancy may not be able to account for levels of postpartum smoking. In such studies (Malloy et al. 1992), the risk estimates for maternal smoking may be underestimated, since many women who quit or reduce the amount they smoke during pregnancy resume or increase their prepregnancy smoking levels after giving birth (Floyd et al. 1993; O'Campo et al. 1995).

Most studies have demonstrated that an increased risk of SIDS is associated with maternal smoking during pregnancy (Bergman and Wiesner 1976; Malloy et al. 1988; Kraus et al. 1989; McGlashan 1989; Bulterys et al. 1990; Haglund and Cnattingius 1990; Mitchell et al. 1991; Schoendorf and Kiely 1992; MacDorman et al. 1997; adjusted ORs for mothers who smoked compared with nonsmokers ranged from 1.4 to 3.0 (Table 5.12). Some studies reported a dose-response relationship, comparing mothers who smoked 1 to 9 cigarettes with those who smoked 10 or more cigarettes per day (Haglund and Cnattingius 1990; MacDorman et al. 1997). However, because very few smokers smoke only during pregnancy and not after delivery, it is nearly impossible to identify the risks associated only with prenatal exposure. Recent studies have begun to examine differences in the risk for SIDS between infants of women who smoke only after giving birth and infants of women who smoke both during pregnancy and after delivery (Mitchell et al. 1991; Schoendorf and Kiely 1992; Klonoff-Cohen 1997). These studies suggest that both prenatal and postpartum exposures to tobacco smoke increase the risk of SIDS. For infants exposed to tobacco only during the postpartum period, ORs were 2.4 (95 percent CI, 1.49–3.83) for blacks and 2.2 (95 percent CI, 1.29–3.78) for whites. For infants exposed during pregnancy and after delivery, ORs were 2.9 (95 percent CI, 2.12–4.04) for blacks and 4.07 (95 percent CI, 3.03–5.48) for whites (Schoendorf and Kiely 1992).

In a study containing more information about passive exposure to tobacco smoke, Klonoff-Cohen (1997) reported a dose-response relationship for postpartum smoking exposures even after adjusting for prenatal smoking levels of the mother. With one person smoking in the infant's room, the OR for SIDS was 3.67 (95 percent CI, 1.66–8.13); two to four persons smoking in the infant's room yielded an OR of 20.91 (95 percent CI, 4.02–108.7). These ORs should be interpreted cautiously given the wide CIs. A dose-response relationship was also demonstrated in this study for the number of cigarettes per day that the infant was exposed to during the postpartum period.

Child Physical and Cognitive Development

Strong associations between maternal smoking during pregnancy and adverse outcomes such as lowered birth weight and IUGR have prompted researchers to investigate the longer-term consequences of smoking during pregnancy on the physical growth and cognitive development of infants, children, and young adults. These studies are difficult to conduct, in part because of the need to consider multiple potential confounding factors that can intervene between pregnancy and the outcome of interest (e.g., family or environmental circumstances). Of particular concern is the effect of a continued exposure to passive smoking in the household on the developing infant or child.

Table 5.12 Studies on the association between maternal smoking and infant mortality

Study	Study period	Population	Definition of smoking
Comstock and Lundin 1967	1953–1903	1,113 infants: 448 live-born infants, 234 stillbirths, and 431 deaths	Mothers were classified as nonsmokers and smokers (smokers included those who abstained during pregnancy)
Rush and Kass 1972	1961–1962	3,370 pregnant women	Smoked at least 1 cigarette daily
Bergman and Wiesner 1976	January 1970–February 1974	142 families: 56 who lost babies to SIDS[a] and 86 control families	• Smoking habits of both parents were ascertained during and after pregnancy • Maternal cigarette use was classified as none, <10, 10–19, or ≥20 cigarettes/day
Meyer and Tonascia 1977	1960–1961	51,490 singletons in 12 hospitals	None, <1 pack, or ≥1 pack/day
Cnattingius et al. 1988	1983–1985	281,808 births to mothers aged 15–44 years	• Nonsmokers (nondaily smokers) • 1–9 cigarettes/day • ≥10 cigarettes/day
Malloy et al. 1988	1979–1984	395,730 white live-born singletons, including 2,720 infant deaths	Maternal smoking status during pregnancy was classified as nonsmokers, smoked <1 pack/day, or ≥1 pack/day

[a]SIDS = Sudden infant death syndrome.
[b]RR = Relative risk.
[c]OR = Odds ratio.

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Key results
• Maternal smoking during pregnancy was associated with an increased risk of death for the child • Findings indicate that some characteristics associated with smoking must be responsible for increased neonatal mortality rates rather than smoking per se • Many of the increased hazards for children of smoking mothers appeared to be associated with decreased birth weight
• Cot[illegible] African[illegible] had a perinatal mortality rate almost [illegible] rate ratios [illegible] American nonsmokers) • Afric[illegible] n 865 ex[illegible] lower African American nonsmokers, white smok[illegible] rate of 17% compared with white nonsmokers • Afric[illegible] African American women had infants of lower birth weight. African Ame[illegible] for gestation periods
• A higher proportion of mothers who lost their children to SIDS had smoked both during pregnancy (61 vs. 42%) *and after their babies were born (59 vs. 37%) compared with mothers who did not smoke* • SIDS mothers smoked a significantly greater number of cigarettes than controls • Exposure of infants to cigarette smoke (passive smoking) appears to enhance the risk of SIDS for reasons not known
• Increases in sm[illegible] associated with increases in the frequency of early fetal death and of neonatal de[illegible] ure delivery • These deaths w[illegible] th smoking related increases in the incidence of bleeding during pregnancy, abruptio placentae, placenta previa, and premature rupture of membranes
• Smokers aged <35 years had a RR of late fetal deaths ranging from 1.1 to 1.6, while the risk doubled if the mothers were aged ≥35 years and smoked • Late fetal death rates would be reduced by 11% and early neonatal mortality by 5% if smoking could be eliminated from the pregnant population • Smoking may be the most important preventable risk factor for late fetal deaths
• The association of smoking was higher with postneonatal deaths than with neonatal deaths (adjusted OR[1] = 1.61 vs. 1.17) • The association with smoking was varied by cause of death and was particularly high for respiratory disease [illegible] = 1.9) • Find[illegible] d deaths and SIDS deaths may be related to the effects on the infant of pass[illegible] se after birth

Table 5.12 Continued

Study	Study period	Population	Definition of smoking
Kraus et al. 1989	1959–1966	2,132 infants: 202 cases of SIDS[a] and 1,930 controls who survived the first year of life	• Nonsmokers • >10 cigarettes/day
McGlashan 1989	1980–1986	69,435 live infants	Maternal smoking classified as 0, <10 cig[illegible] [illegible] repres[illegible] cigarettes/day for each [illegible] gories: whether [illegible] normally a smo[illegible] smoked during [illegible] whether she smo[illegible] baby's first year of life
Butler's et al. 1990	1959–1966	2,123 infants: 193 cases of SIDS and 1,930 controls	Women were classified by the number of cigarettes/day during pregnancy (0, <10, or ≥10)
Hagglund and Cnattingius 1990	1983–1985	279,938 infants surviving the first week of life	• Non[illegible] nonsmokers • Moderate smokers: 1–9 cigarettes/day • Heavy smokers: ≥10 cigarettes/day
Mitchell et al. 1991	November 1987–October 1988	631 infants: 128 cases of SIDS and 503 controls	Maternal smoking was assessed by (1) obstetric records, where any amount of smoking was recorded as "yes," and (2) parental interview that recorded whether the mother had smoked cigarettes in the last 2 weeks and if "yes," the number of cigarettes/day
Cnattingius et al. 1992	1983–1987	173,715 nulliparous Nordic women aged ≥20 years who delivered singletons	• No smoking • 1–9 cigarettes/day • ≥10 cigarettes/day

[a]SIDS = Sudden infant death syndrome.
[b]CI = Confidence interval.

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Key results
• Maternal smoking, maternal anemia during pregnancy, and lack of early prenatal care were all positively associated with SIDS
• A positive trend in SIDS risks with increasing numbers of cigarettes smoked during pregnancy remained after adjusting for birth weights
• The unadjusted OR for maternal cigarette smoking during pregnancy was 1.6 (95% CI[a], 1.1–2.5) for >10 cigarettes/day vs. nonsmoking; cigarette smoking was stratified under different categories for different analyses
• Cigarette smoking by parents leading to passive exposure of the baby carried a high RR of SIDS (RR = 4.0)
• If the mother was a habitual smoker, the risk of SIDS was very high (RR = 2.98), the risk was also very high if the mother smoked during pregnancy (RR = 3.32)
• A dose-response relationship between cigarette smoking and increases in the risk of SIDS is suggested
• Infants born to mothers who smoked ≥10 cigarettes/day and who were anemic during pregnancy were at a higher risk of SIDS than infants born to mothers who did not smoke and were not anemic (OR = 4.0 [95% CI, 2.1–7.4])
• Smoking ≥10 cigarettes/day vs. none increased the risk of SIDS by 70% among women with hematocrits >30%, but the risk increased threefold among women with hematocrits <30%
• A low hematocrit was not a risk factor for SIDS among nonsmokers, but became an important predictor among heavy smokers
• Maternal smoking was strongly related to SIDS even while controlling for other risk factors
• Smoking ≥5 cigarettes/day doubled the risk of SIDS, and smoking ≥10 cigarettes/day tripled the risk of SIDS, compared with nonsmokers
• Early SIDS: 7 to 67 days; late SIDS: 68 to 145 days. Logistic regression of the difference between early and late SIDS (based only on SIDS cases) showed that moderate maternal smoking was strongly associated with an increased risk of early SIDS (RR = 1.7 [95% CI, 1.2–2.1])
• Three risk factors were significantly associated with SIDS: maternal smoking, prone sleeping position of baby, and breastfeeding
• The ORs associated with maternal cigarette smoking, compared with no maternal smoking, were as follows: 1–9 cigarettes/day, OR = 1.87 (95% CI, 0.98–3.54); 10–19 cigarettes/day, OR = 2.64 (95% CI, 1.47–4.74); ≥20 cigarettes/day, OR = 5.06 (95% CI, 2.86–8.95)
• These three risk factors may account for an estimated 79% of SIDS deaths
• Women who were nonsmokers and those who had cohabited with the infant's father had the lowest rates of late fetal and early neonatal deaths
• Delayed childbearing among nulliparous women with uncomplicated pregnancies was associated with increased risks of poor pregnancy outcomes

Table 5.12 Continued

Study	Study period	Population	Definition of smoking
Malloy et al. 1992	1980–1985	2,271 infants: 757 cases of SIDS[a] and 1,514 living controls	Packs of cigarettes/day
Schoendorf and Kiely 1992	1988	10,000 births and 6,100 infant deaths from a national maternal and infant health survey	• Nonexposed group: infants whose mothers did not report cigarette smoking either during pregnancy or at the time of the survey • Passive exposure group: infants whose mothers reported smoking at the time of the survey but not during pregnancy • Combined exposure group: infants whose mothers reported smoking at the time of the survey and during pregnancy
Little and Weinberg 1993	1980	4,667 births: 2,832 live-born infants and 1,835 stillbirths	Daily cigarette smoking during pregnancy (none, 1–19, 20–29, ≥30)
Raymond et al. 1994	1963–1986	638,242 pregnancies ≥28 weeks of gestation in Nordic citizens aged ≥20 years	Women were nonsmokers, smoked 1–9 cigarettes/day, and ≥10 cigarettes/day
Klonoff-Cohen et al. 1995	1989–1992	400 parents of infants: 200 whose infants died of SIDS and 200 controls who delivered healthy infants	Smoking status of both parents and other live-in adults during pregnancy and after childbirth was ascertained to determine a child's exposure to tobacco smoke
Stick et al. 1996	Data were not reported	500 healthy infants of mothers participating in a cohort study	Mothers were never smokers, smoked <10 cigarettes/day, and ≥10 cigarettes/day

[a]SIDS = sudden infant death syndrome.
[b]tPTEF/tE = Time to peak tidal expiratory flow as a proportion of expiratory time.

PM3003724085

Source: https://www.industrydocuments.ucsf.edu/docs/zkmj0001

Key results
• In the Missouri study population, there was evidence of a dose-response relationship between smoking during pregnancy and the incidence of SIDS*
• Data from the National Institute of Child Health and Human Development did not support a dose-response relationship
• Neither data set supported a relationship between the age of occurrence of SIDS and smoking during pregnancy
• The benefits of promoting smoking reduction as a means of reducing the occurrence of SIDS remains to be determined
• Infants who died of SIDS were more likely to be exposed to maternal cigarette smoke than were surviving infants
• After adjusting for demographic risk factors, the OR for SIDS among normal birth weight infants was approximately 2 for passive exposure and 3 for combined exposures for both black and white infants
• The results suggest that both intrauterine and passive tobacco smoke exposures are associated with an increased risk of SIDS, and are further inducements to encourage smoking cessation among pregnant women and families with children
• Factors for mothers that appeared to increase the risks of a stillbirth were age ≥35 years, black race, smoking up to 29 cigarettes daily, first delivery, and high body mass
• Smoking 1–29 cigarettes was associated with an increased risk of stillbirth, but smoking ≥30 cigarettes/day appeared to be protective
• One possible explanation for the protective effect of heavy smoking could be that heavily exposed and susceptible fetuses die earlier and are lost before 28 weeks
• Older women [illegible] cigarette women had elevated risks of stillbirths
• There was a do[illegible]oking and the risk of stillbirth, with the risk increasing with the [illegible] OR = 1.2 [95% CI, 1.02–1.4,] ≥10 cigarettes OR = 1.6 [95% CI, 1.4 [illegible]
• The association between smoking [illegible] explained entirely by the higher incidence of growth retardation and placental complications
• Infants who died from SIDS were significantly more likely to be exposed to passive smoke from the mother (OR = 2.28), father (OR = 3.46), or other live-in adults (OR = 2.18) than were control infants
• A dose-response relationship was observed indicating an increase in the risk of SIDS associated with an increase in the child's exposure to tobacco smoke in the first year of life
• Breastfeeding was protective against SIDS among nonsmokers (OR = 0.37) but not smokers (OR = 1.38)
• In utero smoke exposure, a family [illegible] of asthma, and maternal hypertension during pregnancy were [illegible] an after birth
• [illegible] tionship of maternal smoking on IPEH/CE infants of mothers [illegible] west mean IPEH/CE, and infants of nonsmoking mothers had [illegible]

Table 5.12 Continued

Study	Study period	Population	Definition of smoking
MacDorman et al. 1997	United States: 1990–1991 Sweden: 1983–1992	Linked birth and death records for more than 1 million infants	• Nonsmokers: nondaily smokers • Moderate smokers: 1–9 cigarettes/day • Heavy smokers: ≥10 cigarettes/day
Srivastava 1997	1978–1990	176,843 women	Women were asked if they used tobacco during pregnancy (yes/no) and the number of cigarettes/day (0, <1 pack, ≥1 pack)

*SIDS = Sudden infant death syndrome.

Although rates of reducing and quitting smoking during pregnancy are substantial, many women (approximately 70 percent) resume smoking once their infant is delivered (USDHHS 2001). Overpeck and Moss (1991) studied maternal smoking during pregnancy and the exposure to secondhand smoke of children aged five years and younger by mothers and other household members, and found that only 1.2 percent of children were exposed to tobacco smoke prenatally but not postpartum. Thus, a comparison group of infants who had been exposed to smoking during pregnancy but not after delivery is rarely available, making it difficult to attribute any observed effects to prenatal smoking alone.

The mechanisms by which maternal smoking during pregnancy may lead to compromised physical and cognitive development are not clear. However, regarding cognitive development, effects of smoking, and nicotine in particular, on central nervous system development have been proposed. Alterations in the peripheral autonomic pathways, mentioned earlier, may lead to an increased susceptibility to hypoxia-induced short-term and long-term brain damage (Slotkin 1998).

Several studies have examined the association between prenatal maternal smoking and subsequent physical growth of the infant or child, with mixed findings (Goldstein 1971; Rantakallio 1983; Barr et al. 1984; Fogelman and Manor 1988; Eskenazi and Bergman 1995) (Table 5.13). Goldstein (1971) observed the growth of approximately 15,000 seven-year-olds and reported that maternal smoking during pregnancy resulted in a 0.6 cm reduction in height after accounting for social class, birth weight, and gender. In a large birth cohort, Rantakallio (1983) observed a 0.4 to 0.6 cm reduction in height at 14 years of age in children of mothers who smoked compared with children whose mothers were nonsmokers. Neither study adjusted for postpartum smoking. Barr and colleagues (1984) examined associations between maternal smoking during pregnancy and infant size at eight months (weight, length, and head circumference) and reported no differences between infants of smokers and infants of nonsmokers. Fox and colleagues (1990) examined the growth of children at three years of age in relation to prenatal smoking; after adjusting for multiple confounders including postpartum smoking, they found no differences in height and weight. In a study of 2,622 children, Eskenazi and Bergman (1995) found that pregnancy serum cotinine levels when divided into low, medium, and high tertiles were associated with a -3 cm, -3 cm, and -8 cm reduction in the heights, respectively, of children of mothers who had smoked during pregnancy compared with children of nonsmoking mothers. These authors reported that this effect was largely due to a prenatal exposure rather than to a postpartum secondhand smoke exposure.

Studies examining associations between maternal smoking during pregnancy and the child's cognitive development also have reported mixed results.

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Key results

- There was a strong association between maternal smoking and SIDS* for mothers who smoked 1–9 cigarettes/day during pregnancy compared with nonsmokers (adjusted OR = 1.6–2.5), and for mothers who smoked ≥10 cigarettes/day during pregnancy (adjusted OR = 2.3–3.8)
- SIDS rates increased with the amount smoked for all U.S. and Swedish racial and ethnic groups
- Smoking is one of the most important preventable risk factors for SIDS, and smoking prevention programs have the potential to substantially lower SIDS rates

- The RR of low birth weight in the second pregnancy compared with not smoking during either pregnancy was 1.82 for those who smoked during the second pregnancy only and 1.81 for those who smoked during both pregnancies
- The highest risk of fetal mortality (RR = 1.78) occurred among mothers who did not smoke during the first pregnancy but who smoked ≥1 pack/day during the second pregnancy
- Women with the highest RR (1.65) for neonatal deaths were those who reduced their smoking during the second pregnancy but did not stop

Several studies reported associations with smoking during pregnancy and subsequent cognitive development, behavioral outcomes, and educational achievements of infants and children of varying ages (Rantakallio 1983; Naeye and Peters 1984; Sexton et al. 1990) (Table 5.13). Many studies adjusted for several potentially important confounders, and six reported a dose-response relationship (Fogelman and Manor 1988; Weitzman et al. 1992; McCartney et al. 1994; Fried et al. 1997, 1998; Obel et al. 1998) (Table 5.13). The outcomes examined in these studies were babbling abilities in eight-month-old infants, performances on standardized tests of cognitive abilities in school-age children, auditory processing in school-age children, behavioral problems as reported by parents and teachers, and educational achievements of young adults. A few studies had information on both prenatal and postpartum smoking by mothers and parents; two of these studies reported that a prenatal but not a postpartum secondhand smoke exposure was associated with adverse outcomes (Weitzman et al. 1992; McCartney et al. 1994). Yet, in both studies, prenatal and postpartum smoking was significantly associated with adverse developmental outcomes. Many studies examined multiple outcomes, and not all were significantly associated with smoking during pregnancy. Overall, observed differences between smokers and nonsmokers were relatively small.

Three studies reported no association between maternal smoking during pregnancy and adverse cognitive or behavioral outcomes (Fergusson and Lloyd 1991; Baghurst et al. 1992; Eskenazi and Trupin 1995). Fergusson and Lloyd (1991) studied children aged 12 years and adjusted for several potential confounders, including postpartum smoke exposure. Once confounders were accounted for, no differences between children of mothers who smoked and children of mothers who did not smoke during their pregnancies were observed. In a study of more than 2,000 five-year-old children, Eskenazi and Trupin (1995) found that active smoking during pregnancy did not result in cognitive deficits in children according to results from the Raven Colored Progressive Matrices Test and the Peabody Picture Vocabulary Test at five years of age. Thus, studies on cognitive development and behavioral problems report small or no differences among children of pregnant smokers compared with children of pregnant nonsmokers. Confounding by unmeasured factors cannot be ruled out as an explanation for the small differences, which may not be clinically meaningful.

Evidence Synthesis

The evidence on the relationship between maternal smoking during pregnancy and congenital malformations is mixed. Most studies report no association between maternal smoking and congenital malformations as a whole. This finding is not unexpected, as it is unlikely that smoking during pregnancy would be linked to all of the multiple etiologic pathways involved in the various malformations.

Table 5.13 Studies on the association between maternal smoking and cognitive development, behavioral problems, and growth in children

Study	Study period	Population	Definition of smoking
Goldstein 1971	1958–1965	14,848 children aged 7 years	Smoking status after the fourth month of pregnancy: • None • Medium: 1–10 cigarettes/day • Heavy: >10 cigarettes/day
Rantakallio 1983	1966–1981	3,688 children: 1,844 had mothers who smoked during pregnancy and 1,844 controls	• Light smokers: smoked ≤10 cigarettes/day • Heavy smokers: smoked >10 cigarettes/day at the end of the second month of pregnancy
Barr et al. 1984	NR*	453 infants 8 months of age	Average nicotine use was calculated by multiplying the number of cigarettes/day by nicotine content of the brand used by each woman
Naeye and Peters 1984	1959–1976	9,024 children	• Nonsmokers • Light smokers: 1–19 cigarettes/day • Heavy smokers: ≥20 cigarettes/day
Fogelman and Manor 1988	1958–1981	8,200 young adults aged 23 years	Number of cigarettes/day smoked after the fourth month of pregnancy (0, 1–9, 10–19, ≥20)
Sexton et al. 1990	NR	364 children 3 years of age	• Women who smoked >10 cigarettes/day at the beginning of pregnancy were recruited and followed. At the eighth month, they were classified either as quitters or smokers • Quitters quit smoking during the pregnancy • Smokers smoked throughout the pregnancy

*NR = Data were not reported.

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Source: https://www.industrydocuments.ucsf.edu/docs/zkmj0001

Key results

- Nonsmoking mothers had children 0.6 cm taller than those of heavy smoking women
- If birth weight is excluded from the analysis, the difference in height between the two groups rises to 1.0 cm
- Smoking during pregnancy influences height partly by lowering the birth weight, and partly by an effect over and above its effect on birth weight

- Children of smokers were more prone to respiratory diseases, were shorter, and did not perform as well in school compared with controls
- Smoking mothers differed from controls in social class and health status and were more often unemployed and without families. Even when these factors were taken into account, maternal smoking had an effect on the children's physical and mental development

- Maternal smoking during pregnancy was not significantly related to infant size at 8 months
- At birth, nicotine exposure was more strongly associated with infant size than was alcohol exposure, but by 8 months most of the nicotine effects had dissipated and alcohol, not nicotine, remained significantly related to infant size at 8 months

- Hyperactivity, short attention span, and lower scores on spelling and reading tests were more frequent for children whose mothers had smoked throughout pregnancy
- Cogn[illegible] achievement test scores only 2 to 4% lower in children whose mot[illegible]
- Fetal [illegible] oral abnormalities in children of smokers

- There was weak evidence for a relationship between smoking during pregnancy and self-reported heights of the offspring after several confounding variables were controlled for, but the article does not specify if the offspring are shorter or taller
- The average difference in height between children whose mothers smoked ≥20 cigarettes/day during the second half of pregnancy and those whose mothers did not was 0.93 cm in males and 1.83 cm in females
- The relation of smoking during pregnancy with educational achievements of the offspring, measured by the highest qualification achieved, was strong after controlling for confounding factors

- Children whose mothers quit sm[illegible] with those whose mothers continued to smoke performed at a statistically significant [illegible] cognitive tests
- Statistical adjustments f[illegible] factors, characteristics of the child, and fetal maturity did not account for these observ[illegible]
- Findings suggest that q[illegible] becoming pregnant may prevent some cognitive damage to the fetus

Table 5.13 Continued

Study	Study period	Population	Definition of smoking
Bauman et al. 1991	1960–1967	19,044 children born to women enrolled in a health plan	• Whether the mother or her husband smoked cigarettes at the time of the examination • Average number of cigarettes/day by both parents
Fergusson and Lloyd 1991	NR	A birth cohort of children followed for 12 years (1,265 at birth, reduced to 1,070 at 12 years due to attrition)	Maternal cigarette smoking during pregnancy was measured by an estimated typical daily cigarette use for each trimester (0, 1–10, 11–20, >20)
Baghurst et al. 1992	May 1979–May 1982	548 children from a cohort study	Nonsmokers had never smoked, or had smoked no more than five cigarettes during the pregnancy
Weitzman et al. 1992	1979–1986	NR	• Maternal smoking status: ≤1 pack/day or >1 pack/day • Children's exposure: prenatal only (mother smoked only during pregnancy) • Passive only (mother smoked only after pregnancy) • Prenatal plus passive
Fergusson et al. 1993	1977–1992	1,265 children	• During pregnancy: mean number of cigarettes/day during each trimester • After pregnancy: estimated average daily cigarette use of the mother from the child's birth to 5 years of age
Olds et al. 1994	April 1978–September 1980	400 families: mothers and their children	Maternal prenatal smoking classified by cigarettes smoked/day (0, 1–9, ≥10)

CI = Confidence Inter[illegible] al.

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Key results

- Parental smoking was associated with children's performance on at least one cognitive measure, and the effect persisted after the inclusion of controls
- Children of parents who were smokers but had quit by the time of the examination performed better than children whose smoking parents continued to smoke
- There was a dose-response relationship between parental smoking and cognitive performance

- Children whose mothe[illegible] pregnancy scored significant[illegible] reduced tests of intelligence, reading, an[illegible] ability than children whose m[illegible]
- After adjusting for con[illegible], there was no detectable re[illegible] maternal smo[illegible]
- Resu[illegible] we[illegible] caused effect on children's cognitive ability, which may be influ[illegible] environment from which these children come

- Differences in mean developmental test scores between children whose mothers smoked and those whose mothers did not smoke differed slightly
- The results were not statistically significant when adjusted for socioeconomic status, quality of home environment, and the mother's intelligence, suggesting that social and environmental factors are major confounders of the association between exposure to maternal smoking and neuropsychological development in childhood

- Children's be[illegible] exposures to maternal cigarette smoking, with evidence sugg[illegible]
- Children who[illegible] after pregnancy had 1.17 additional problems associated with smoking <1 pack/day and 2.01 additional problems associ[illegible] ≥1 pack/day
- Children whose mothers smoked <1 pack/day were 1.41 times as likel[illegible] behavior problem scores and 1.54 times as likely if their mothers smoked ≥1 pack/da[illegible] after pregnancy

- Children whose mothers smoked >20 cigarettes/day had mean problem behavior scores between 0.16 and 0.56 standard deviations higher than those of children whose mothers were nonsmokers
- Smoking after pregnancy was not significantly associated with increased rates of childhood problem behaviors
- Smoking during pregnancy may be associated with small but detectable increases in the risks of problem behaviors in childhood

- Children whose mothers smoked [illegible]y during pregnancy had intellectual test scores that were 4.35 points lower (95% CI [illegible]) than scores of children whose mothers did not smoke during pregnancy
- The greatest difference in childre[illegible]ctioning was found in cigarette smoking measured at the end of pregnancy
- Maternal cigarette smoking during pregnancy poses a major risk for neurodevelopmental impairment among children

Table 5.13 Continued

Study	Study period	Population	Definition of smoking
Eskenazi and Bergmann 1995	1964–1967	2,622 women enrolled in a children's health and development study	• Nonsmokers: women who had never smoked or had quit before pregnancy • Smokers: number of cigarettes/day (0, 1–9, 10–19, 20–29, ≥30)
Eskenazi and Trupin 1995	1964–1967	2,424 children aged 5 years from a children's health and development study	NR
Fried et al. 1997	1978	131 children aged 9–12 years with ascertained prenatal exposures to marijuana and cigarettes	• Smoking during pregnancy was measured by nicotine scores (average number of cigarettes/day multiplied by the nicotine content of the specified brand) • Categorized as nonsmoking, light, or heavy (0 mg nicotine/day, >0 but <16 mg nicotine/day, and ≥16 mg nicotine/day; ≥16 mg nicotine/day = approximately 1 pack of cigarettes of average strength)
Olsen et al. 1998	1991–1992	2,302 singletons without any disability born at a hospital in a 1-year period	• Non[illegible] • 1–9 cigarettes/day • 10–19 cigarettes/day • ≥20 cigarettes/day
Kelmanson et al. 2002	1999–2000	250 singletons aged 2–4 months born during study period	• Maternal smoking during pregnancy (yes/no) • Maternal exposure during pregnancy to others who smoked (yes/no)

[1]OR = Odds ratio.

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Key results

- Children of mothers who were heavy smokers during pregnancy were shorter at 5 years of age than children of nonsmokers
- The effect appears to be attributable to in utero exposure rather than postnatal secondhand smoke exposure during early childhood
- The study was not able to demonstrate whether women who quit smoking during pregnancy can prevent long-term sequelae on growth

- Children whose mothers smoked during pregnancy had somewhat higher adjusted Raven and PPVT (child cognitive development) scores than children of nonsmokers, although they did not differ in activity level
- Children who were exposed to tobacco smoke during childhood had lower adjusted Raven and PPVT scores and were rated more active by their mothers; the differences may be attributed to uncontrolled confounding of sociobehavioral factors
- The possibility that secondhand smoke smoke exposure during childhood may be more hazardous to neurodevelopment than prenatal exposure cannot be ruled out

- There was a dose-dependent relationship between prenatal cigarette exposure and lower language and reading scores of the children
- Maternal exposure to secondhand smoke during pregnancy had no effect on either reading or language outcomes, whereas the child's exposure to secondhand smoke adversely affected language but not reading

- There was a dose-response association between the number of cigarettes/day during pregnancy and habituation abilities of infants
- Smoking ≥10 cigarettes/day during pregnancy almost doubled the risk (OR[a] = 2.0 [95% CI: 1.1–3.6]) of the infant's being a nonhabituator at 8 months of age; the risk was higher for children who were breastfed for less than 4 months (OR = 2.7 [95% CI: 1.3–5.8])

- Infants born to smoking mothers had a higher frequency of low birth weight ($p = 0.031$)
- Smoking during pregnancy was significantly associated with the infant's intensity of reactions ($p = 0.0039$)
- There was no significant association between smoking during pregnancy and infant activity, rhythmicity, approachability, adaptability, mood, persistence, distractibility, and threshold

For selected malformations, oral clefts in particular, several studies have reported positive associations with smoking. The biologic evidence on the etiology in general for oral clefts is scant, therefore making it difficult to establish a causal role of smoking. Recent studies on interactions between genes and the environment are contributing further to understanding the etiology of oral clefts and the role of smoking, but much work is still needed.

The data on maternal smoking and elevated rates of SIDS are abundant and consistent in the literature. However, evidence is not available to determine whether prenatal smoking alone is causally related to SIDS. Studies have demonstrated that prenatal smoking combined with postpartum passive exposure elevates the risk beyond that for a passive exposure to smoking alone. Some data on biologic plausibility are emerging. One hypothesized mechanism is that exposure to cigarette smoke during pregnancy has effects on the fetal respiratory system and the brain that may, in turn, contribute to SIDS.

Studies examining relationships between maternal smoking during pregnancy and subsequent physical growth of the child report mixed findings. Moreover, the magnitude of reported differences between children of smokers and nonsmokers, especially for physical growth, is extremely small. Information on the mechanisms by which the physical and cognitive development of children are affected by exposures to prenatal smoking is not available and potential confounding is a concern.

Conclusions

1. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and congenital malformations in general.
2. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking and oral clefts.
3. The evidence is sufficient to infer a causal relationship between sudden infant death syndrome and maternal smoking during and after pregnancy.
4. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and physical growth and neurocognitive development of children.

Implications

Mothers who smoke increase their children's risk of SIDS substantially; smoking during pregnancy and after the child's birth should be a target for forceful and effective interventions. Future studies of smoking and congenital malformations should selectively build on the accumulating evidence of the few malformations for which there are elevated risks. Although further studies may elucidate the relationship between prenatal smoking and the risk of SIDS, and subsequent physical and cognitive development, study design issues may be too challenging to overcome. Specifically, the challenges are the identification of a sizable group of infants who are only exposed prenatally and the ability to adjust for the multiple confounders that may intervene between pregnancy and infant or child outcomes.

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Conclusions

Fertility

1. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and sperm quality.

2. The evidence is sufficient to infer a causal relationship between smoking and reduced fertility in women.

Pregnancy and Pregnancy Outcomes

3. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and ectopic pregnancy.

4. The evidence is suggestive but not sufficient to infer a causal relationship between maternal active smoking and spontaneous abortion.

5. The evidence is sufficient to infer a causal relationship between maternal active smoking and premature rupture of the membranes, placenta previa, and placental abruption.

6. The evidence is sufficient to infer a causal relationship between maternal active smoking and a reduced risk for preeclampsia.

7. The evidence is sufficient to infer a causal relationship between maternal active smoking and preterm delivery and shortened gestation.

8. The evidence is sufficient to infer a causal relationship between maternal active smoking and fetal growth restriction and low birth weight.

Congenital Malformations, Infant Mortality, and Child Physical and Cognitive Development

9. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and congenital malformations in general

10. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking and oral clefts.

11. The evidence is sufficient to infer a causal relationship between sudden infant death syndrome and maternal smoking during and after pregnancy.

12. The evidence is inadequate to infer the presence or absence of a causal relationship between maternal smoking and physical growth and neurocognitive development of children.

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